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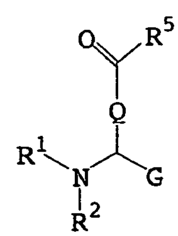
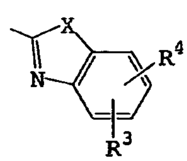
[Continued on next page]

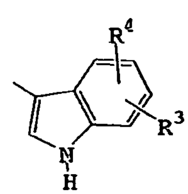
(54) Title: INDOLES, BENZIMIDAZOLES OR NAPHHIMIDAZOLES AS HISZONE DEACETYLASE (HDAC) INHIBITOR



(I)



(I-a)



(I-b)

(57) Abstract: A compound of the following formula (I):whereinR¿1? is acyl, R¿2? is hydrogen, orR¿1? and R¿2? are linked together to form a heterocyclic ring, R¿5? is hydroxy, hydroxylamino, lower alkyl, lower alkoxy, halo(lower)alkyl or hydroxy(lower)alkyl, Q is lower alkylene or lower alkenylene, andG is a substituent selected from the following formulas and wherein R¿3? and R¿4? are each independently hydrogen, halogen, halo(lower)alkyl, cyano, aryl or aryl(lower)alkyl optionally substituted with one or more suitable substituent(s), orR¿3? and R¿4? are linked together to form an aromatic ring, andX is NH, O or S, or a salt thereof. The compound is useful as an inhibitor of histone deacetylase.

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INDOLES, BENZIMIDAZOLES OR NAPHHIMIDAZOLES AS HISTONE DEACETYLASES (HDAC) INHIBITORS

TECHNICAL FIELD

The present invention relates to a compound, which is useful as a medicament, and to a pharmaceutical composition comprising the same.

BACKGROUND ART

Histone deacetylase (hereinafter also referred as HDAC) is known to play an essential role in the transcriptional machinery for regulating gene expression, induce histone hyperacetylation and to affect the gene expression. Therefore, it is useful as a therapeutic or prophylactic agent for diseases caused by abnormal gene expression, such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections, tumors and the like.

SUMMARY OF THE INVENTION

The present invention relates to a novel compound, which is useful as a medicament, and to a pharmaceutical composition comprising the same.

More particularly, the present invention relates to a compound, which has a potent inhibitory effect on the activity of histone deacetylase.

The inventors of the present invention have also found that a histone deacetylase inhibitor, such as compound of formula (I) (hereinafter compound [I]), has a potent immunosuppressive effect and potent antitumor effect. Therefore, a histone deacetylase inhibitor such as compound [I] is useful as an active ingredient of an immunosuppressant and an antitumor agent, and useful as a therapeutic or prophylactic agent for diseases such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections, tumors and the like.

Accordingly, one object of the present invention is to provide a compound, which has biological activities for treating or preventing the diseases as stated above.

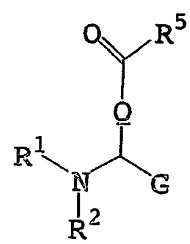
Another object of the present invention is to provide a pharmaceutical composition containing the compound [I] as an active ingredient.

A further object of the present invention is to provide use of the histone deacetylase inhibitors, such as the compound [I], for treating or preventing the diseases as stated above.

A yet further object of the present invention is to provide a commercial package comprising the pharmaceutical composition containing the compound [I] and a written matter associated therewith, the written matter stating that the pharmaceutical composition may or should be used for treating or preventing the diseases as stated above.

Thus, the present invention provides

[1] a compound of the formula (I):



(I)

wherein

R^1 is acyl,

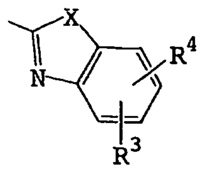
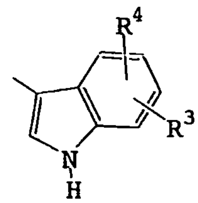
R^2 is hydrogen, or

R^1 and R^2 are linked together to form a heterocyclic ring,

R^5 is hydroxy, hydroxylamino, lower alkyl, lower alkoxy, halo(lower)alkyl or hydroxy(lower)alkyl,

Q is lower alkylene or lower alkenylene, and

G is a substituent selected from the following formulas

 (I-a) and  (I-b)

wherein

R^3 and R^4 are each independently hydrogen, halogen, halo(lower)alkyl, cyano, aryl or aryl(lower)alkyl optionally substituted with one or more suitable substituent(s), or

R^3 and R^4 are linked together to form an aromatic ring, and

X is NH, O or S,

or a salt thereof;

[2] the compound of the above-mentioned [1], wherein

R^1 is acyl selected from the group consisting of arylcarbonyl in which the aryl portion is optionally substituted with one or more suitable substituent(s); heterocyclic carbonyl; lower alkyl-carbonyl; carbamoyl in which the amino portion is optionally mono- or di-substituted with suitable substituent(s); lower alkyl-carbonyloxy(lower)alkylcarbonyl; lower alkoxycarbonyl; lower alkylsulfonyl; and arylsulfonyl,

R^2 is hydrogen, or

R^1 and R^2 are linked together to form a heterocyclic ring,

R^3 and R^4 are each independently hydrogen; halogen; halo(lower)alkyl; cyano; aryl; or aryl(lower)alkyl in which the alkyl portion is optionally substituted with hydroxy or lower alkoxy, or

R^3 and R^4 are linked together to form a benzene ring,

R^5 is hydroxylamino, halo(lower)alkyl or hydroxy(lower)alkyl,

X is NH, and

Q is lower alkylene,

or a salt thereof;

[3] the compound of the above-mentioned [2], wherein

R^1 is arylcarbonyl in which the aryl portion is optionally substituted with one or more substituent(s) selected from the group consisting of lower alkoxycarbonyl; carboxy; lower

alkylcarbamoyl; N, N-di(lower)alkylamino; lower alkyl; hydroxy; and cyano, or a heterocyclic carbonyl,

R^3 and R^4 are each independently hydrogen, or

R^3 and R^4 are linked together to form a benzene ring,

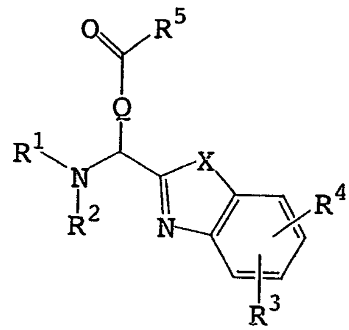
R^5 is hydroxylamino, halo(lower)alkyl or hydroxy(lower)alkyl,

X is NH, and

Q is lower alkylene,

or a salt thereof;

[4] A compound of the following formula (I'):



(I')

wherein

R^1 is acyl,

R^2 is hydrogen, or

R^1 and R^2 are linked together to form a heterocyclic ring,

R^3 and R^4 are each independently hydrogen, halogen, halo(lower)alkyl, cyano, aryl or aryl(lower)alkyl optionally substituted with one or more suitable substituent(s), or

R^3 and R^4 are linked together to form an aromatic ring,

R^5 is hydroxylamino, halo(lower)alkyl or hydroxy(lower)alkyl,

X is NH, O or S, and

Q is lower alkylene or lower alkenylene,

or a salt thereof;

[5] the compound of the above-mentioned [4], wherein

R^1 is acyl selected from the group consisting of arylcarbonyl in which the aryl portion is optionally substituted with one or more suitable substituent(s); heterocyclic carbonyl; lower alkyl-carbonyl; carbamoyl in which the amino portion is optionally mono- or di-substituted with suitable substituent(s); lower

alkyl-carbonyloxy(lower)alkylcarbonyl; lower alkoxycarbonyl; lower alkylsulfonyl; and arylsulfonyl,

R^2 is hydrogen, or

R^1 and R^2 are linked together to form a heterocyclic ring,

R^3 and R^4 are each independently hydrogen; halogen; halo(lower)alkyl; cyano; aryl; or aryl(lower)alkyl in which the alkyl portion is optionally substituted with hydroxy or lower alkoxy, or

R^3 and R^4 are linked together to form a benzene ring,

R^5 is hydroxylamino,

X is NH, and

Q is lower alkylene,

or a salt thereof;

[6] the compound of the above-mentioned [5], wherein

R^1 is arylcarbonyl in which the aryl portion is optionally substituted with one or more substituent(s) selected from the group consisting of lower alkoxycarbonyl; carboxy; lower alkylcarbamoyl; N, N-di(lower)alkylamino; lower alkyl; hydroxy; and cyano,

R^3 and R^4 are linked together to form a benzene ring,

R^5 is hydroxylamino,

X is NH, and

Q is lower alkylene,

or a salt thereof, etc.

Of the above-mentioned compounds, the compounds represented by the formula (I') (compound [I']) is also encompassed in the scope of the compound represented by the formula (I). Hereinafter "compound [I]" also encompasses "compound [I']".

The above-mentioned compounds and salts thereof can be prepared by the processes as illustrated in the following reaction schemes or by the methods disclosed in the Preparations and Examples.

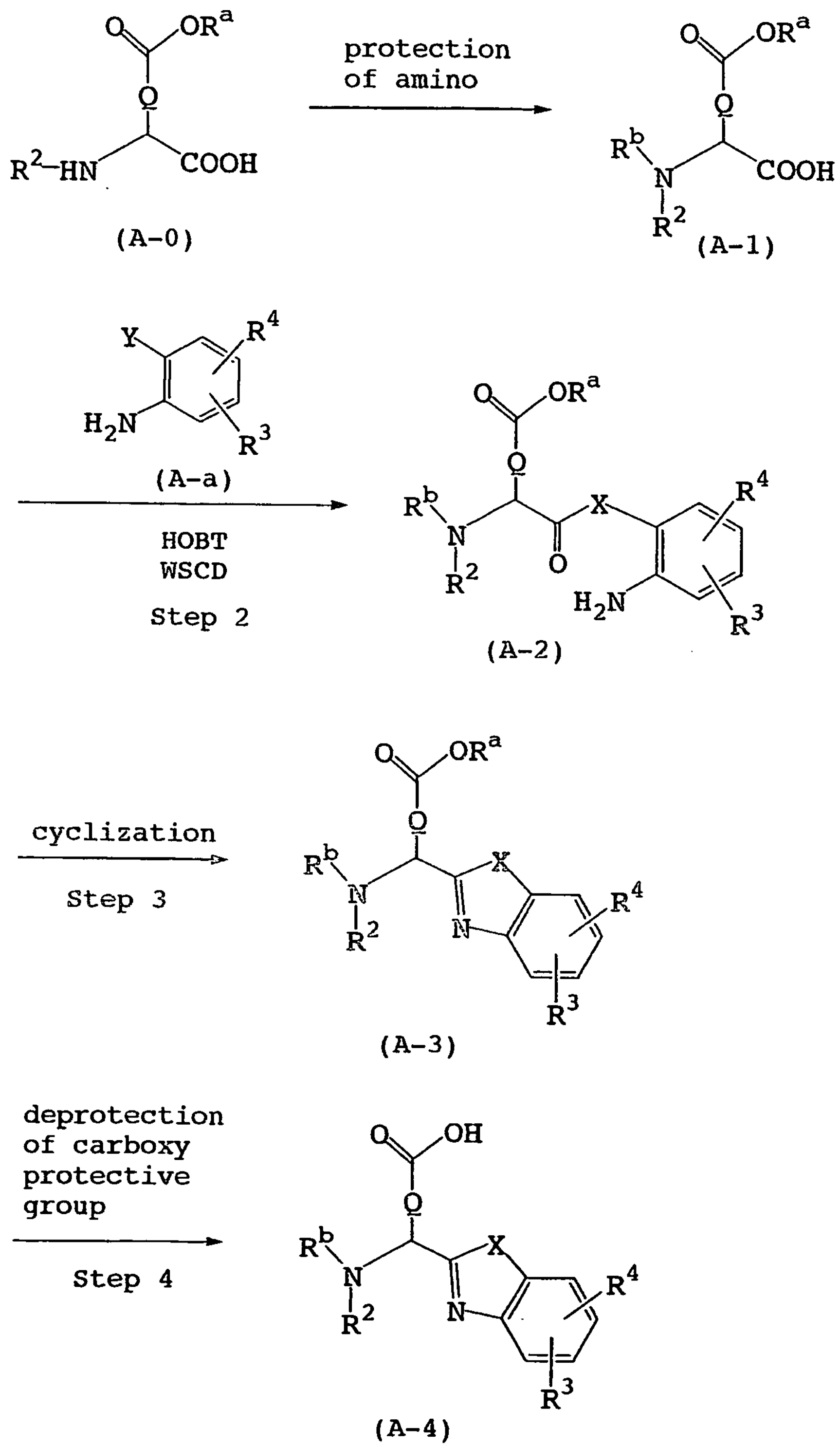
In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various

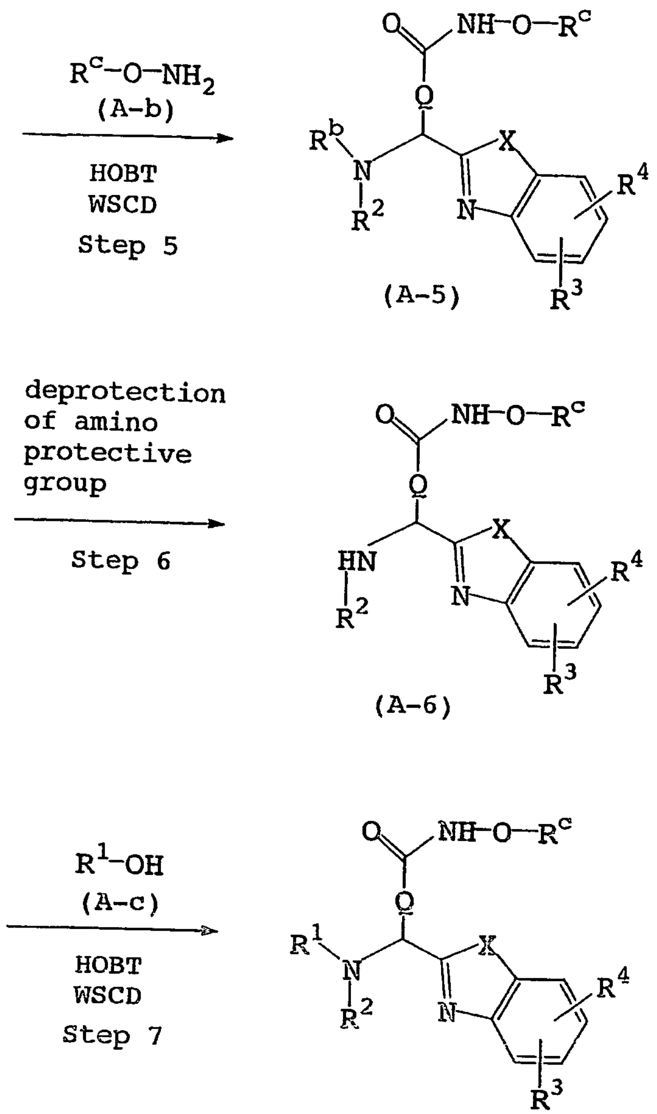
definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The compound [I] or a salt thereof can be prepared by the process as illustrated in the following reaction schemes.

In the following processes, Compounds [I-1], [I-2], [I-3], [I-3'](Compound [I-3] wherein R^5 is lower alkoxy), [I-4], [I-5] and [I-6] are encompassed in the scope of the Compound [I], and Compounds [II-1] to [II-10] are encompassed in the scope of Compound [II]. Compounds [III-1] and [III-2] are encompassed in the scope of the Compound [III], and Compounds [V-1] and [V-2] are encompassed in the scope of the Compound [V].

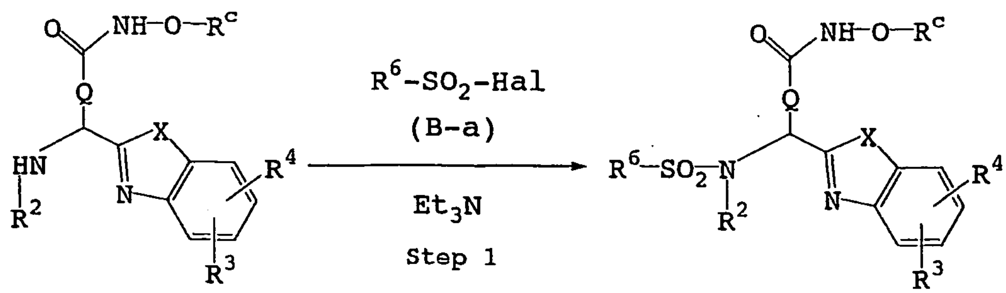
Process A


protection
of amino
(A-0)
(A-1)
(A-a)
HOBT
WSCD
Step 2
(A-2)
cyclization
Step 3
(A-3)
deprotection
of carboxy
protective
group
Step 4
(A-4)


R^c-O-NH2
(A-b)
HOBT
WSCD
Step 5
(A-5)
deprotection of amino protective group
Step 6
(A-6)
R^1-OH
(A-c)
HOBT
WSCD
Step 7

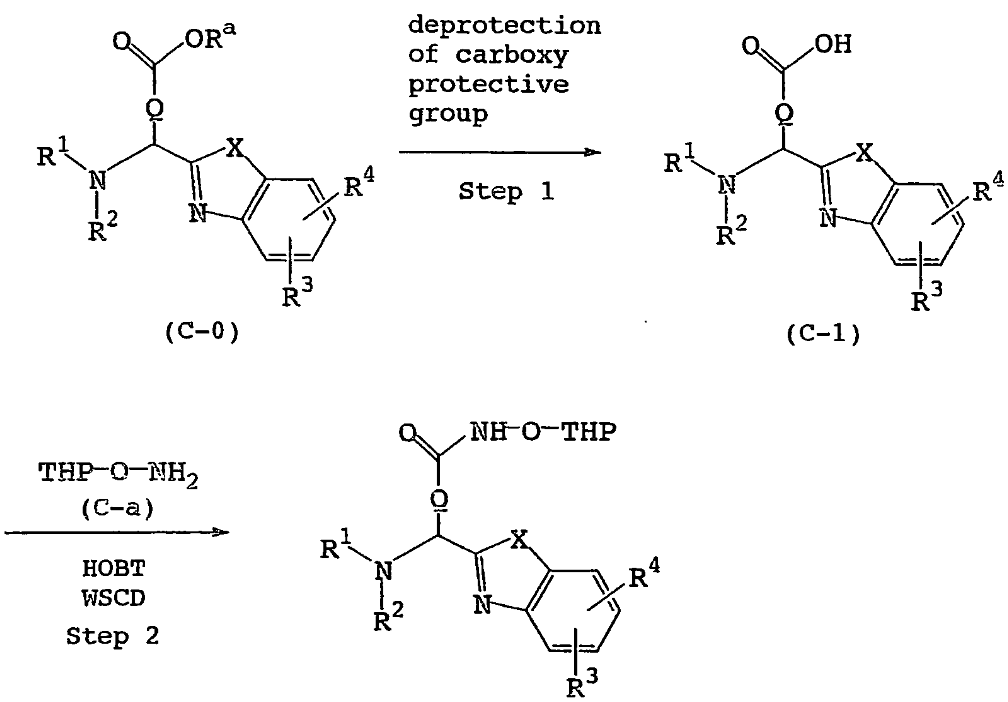
[II-1]

Process B



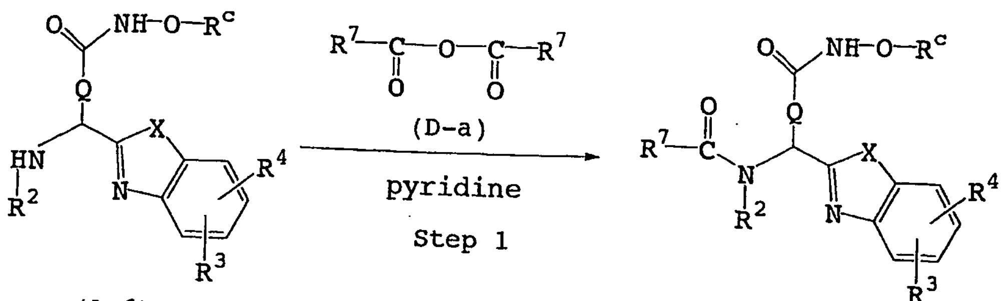
(A-6) [II-2]

Process C



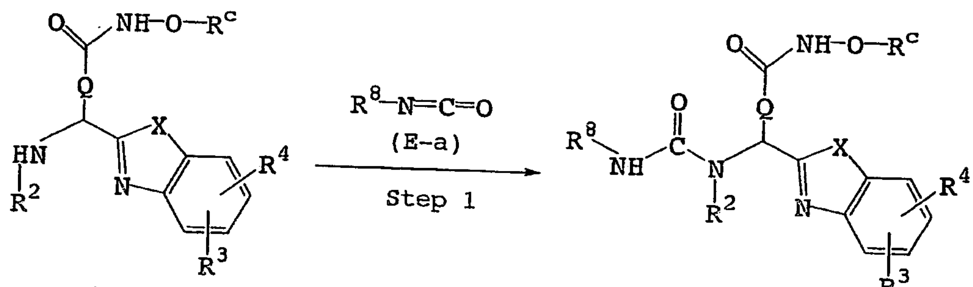
(C-0) (C-1) [II-3]

Process D



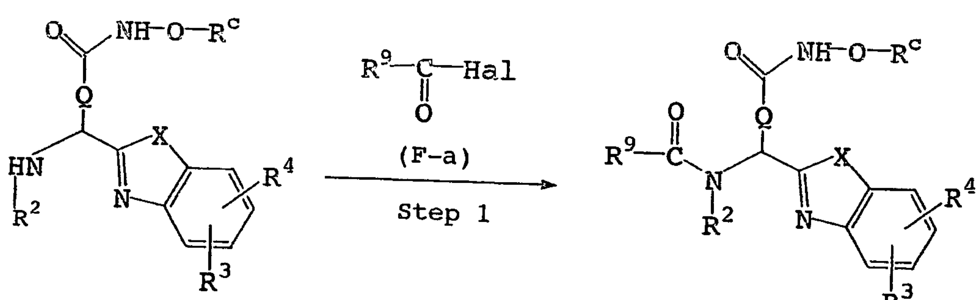
(A-6) [II-4]

Process E



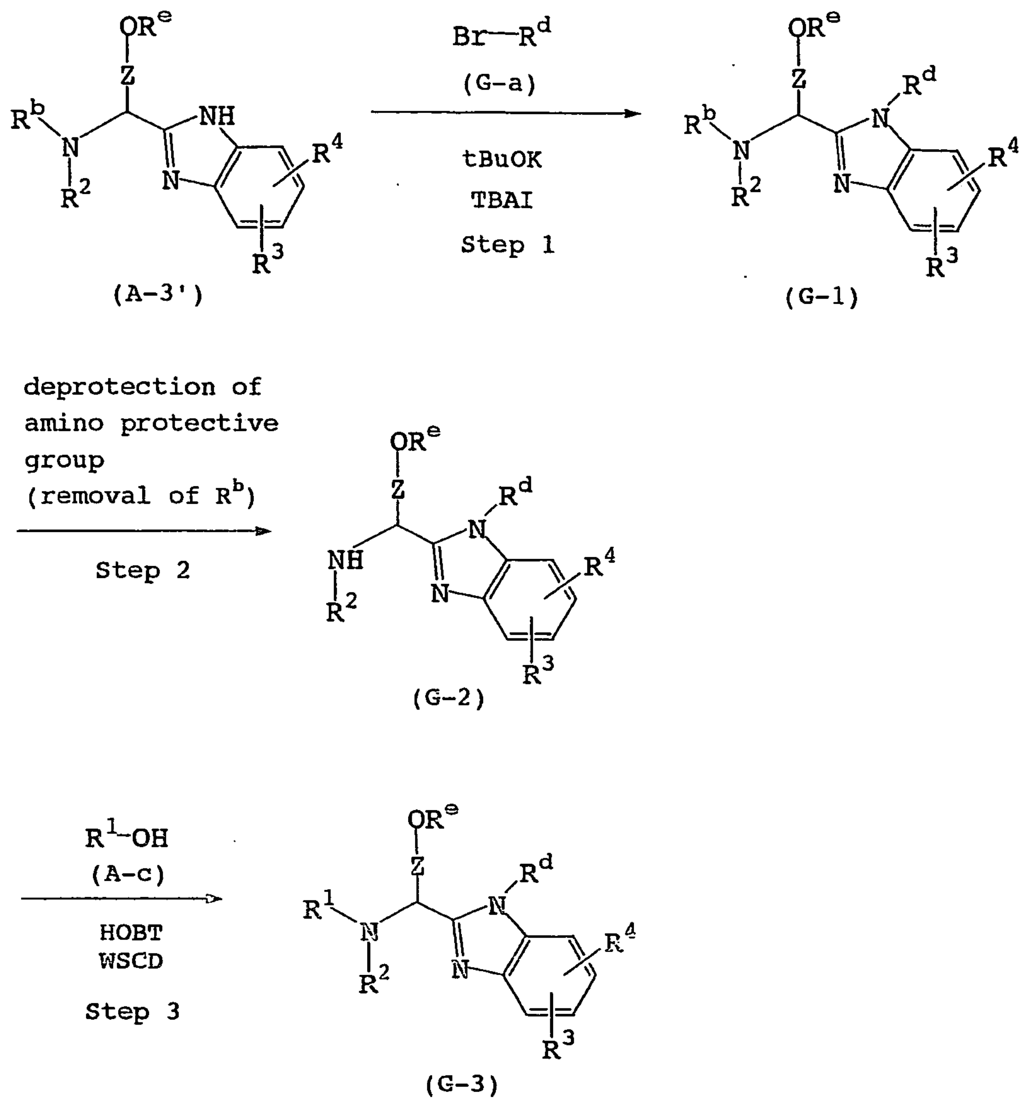
(A-6) [II-5]

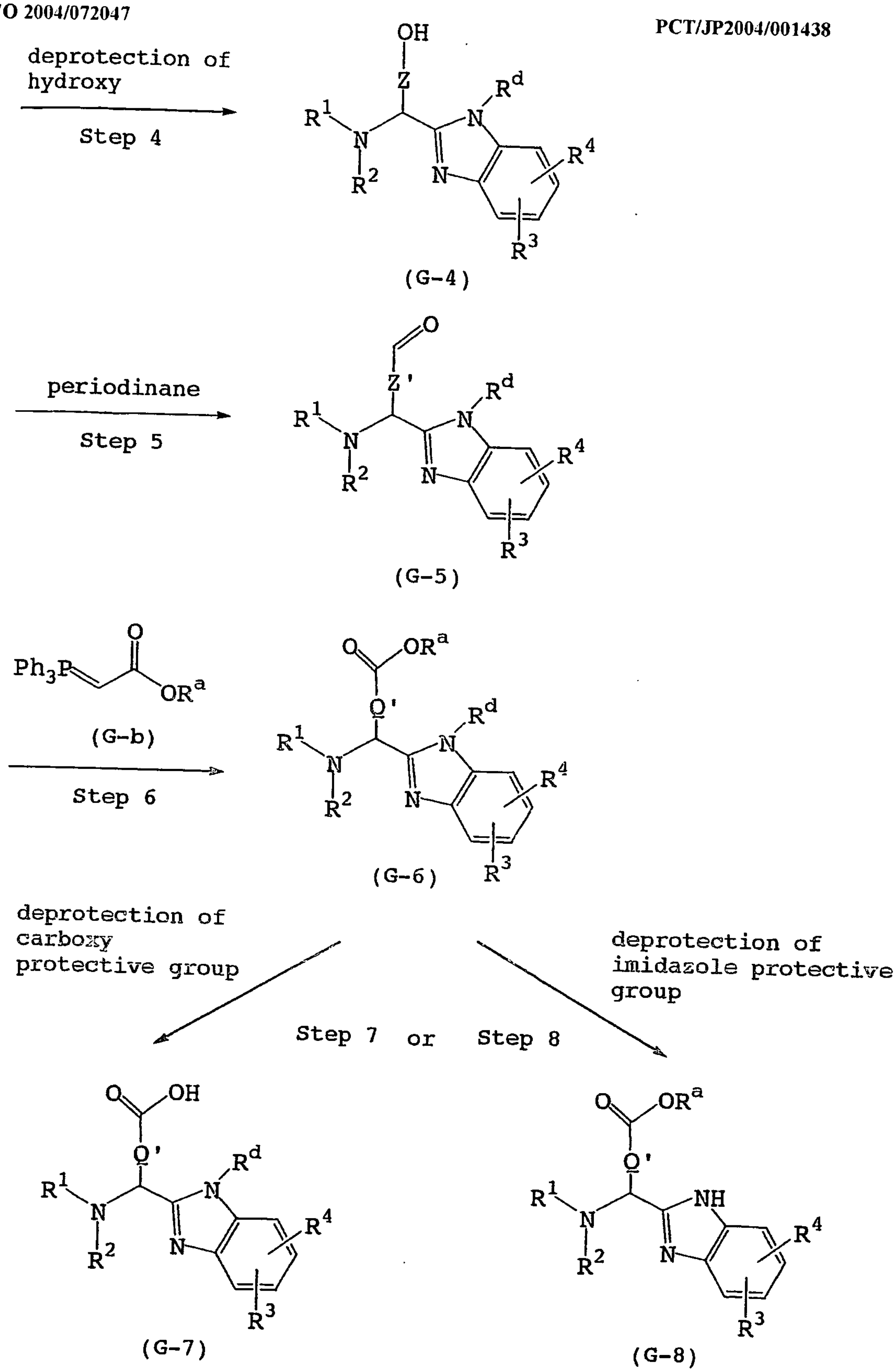
Process F

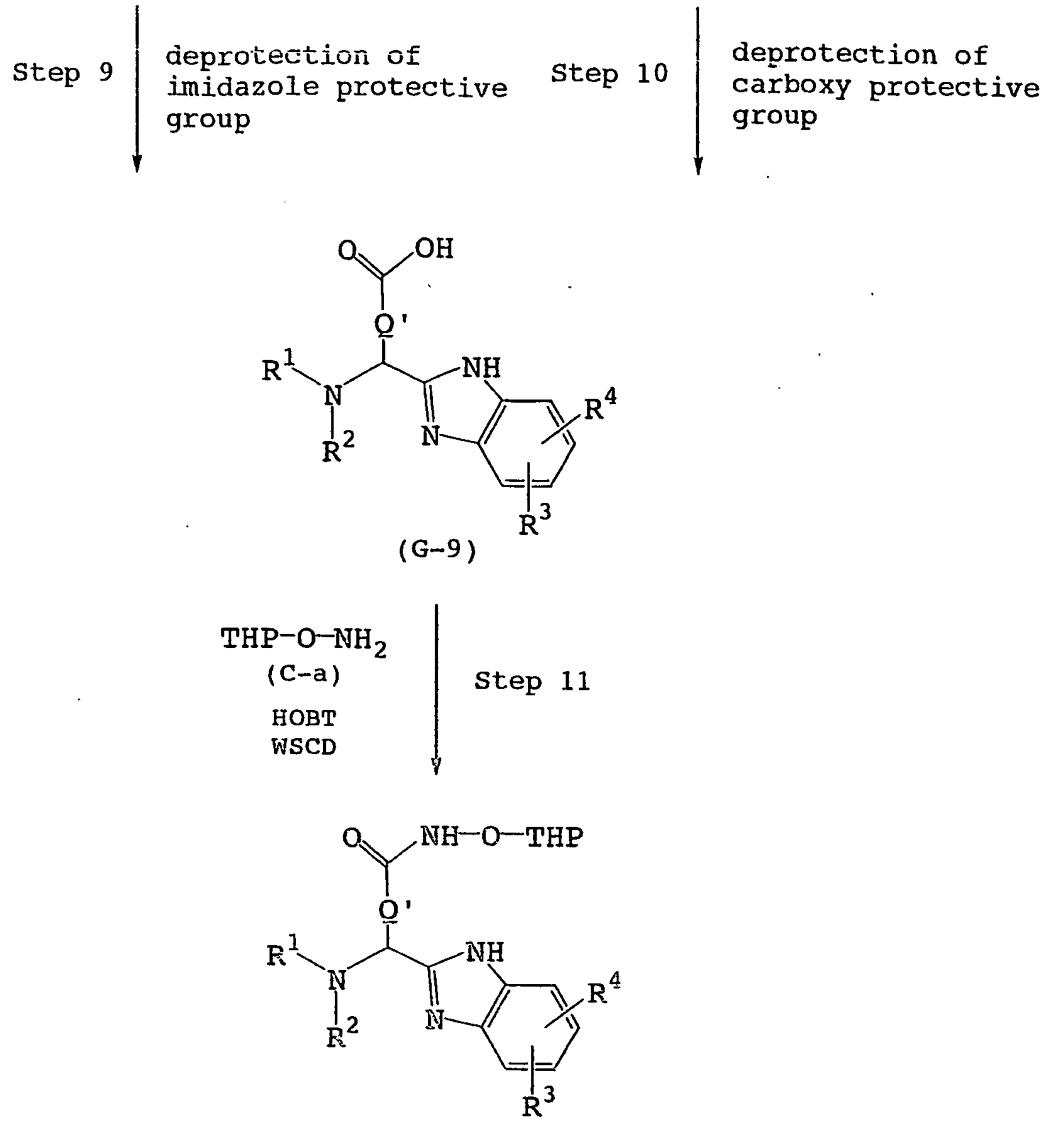


(A-6) [II-6]

Process G

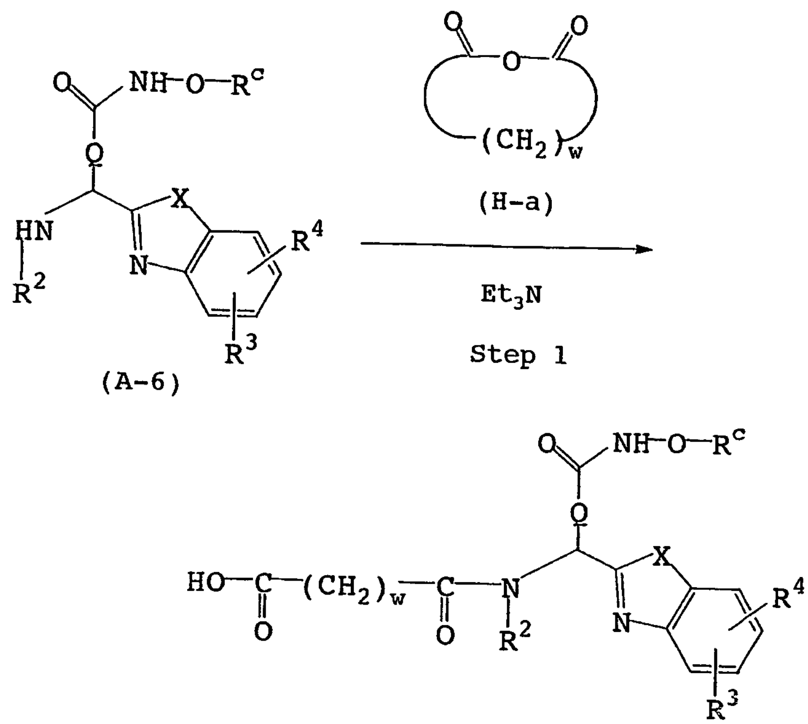

Br—Rd
(G-a)
tBuOK
TBAI
Step 1
(A-3')
(G-1)
deprotection of amino protective group (removal of Rb)
Step 2
(G-2)
R1-OH
(A-c)
HOBT
WSCD
Step 3
(G-3)


deprotection of hydroxy
Step 4
(G-4)
periodinane
Step 5
(G-5)
(G-b)
Step 6
(G-6)
deprotection of carboxy protective group
Step 7 or Step 8
deprotection of imidazole protective group
(G-7)
(G-8)


Step 9
deprotection of imidazole protective group
Step 10
deprotection of carboxy protective group
(G-9)
THP-O-NH2
(C-a)
HOBT
WSCD
Step 11

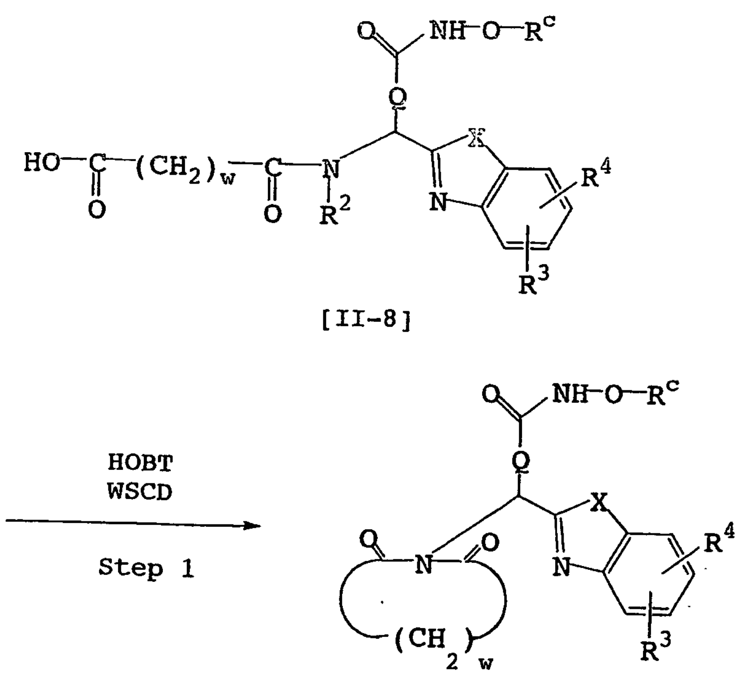
[II-7]

Process H



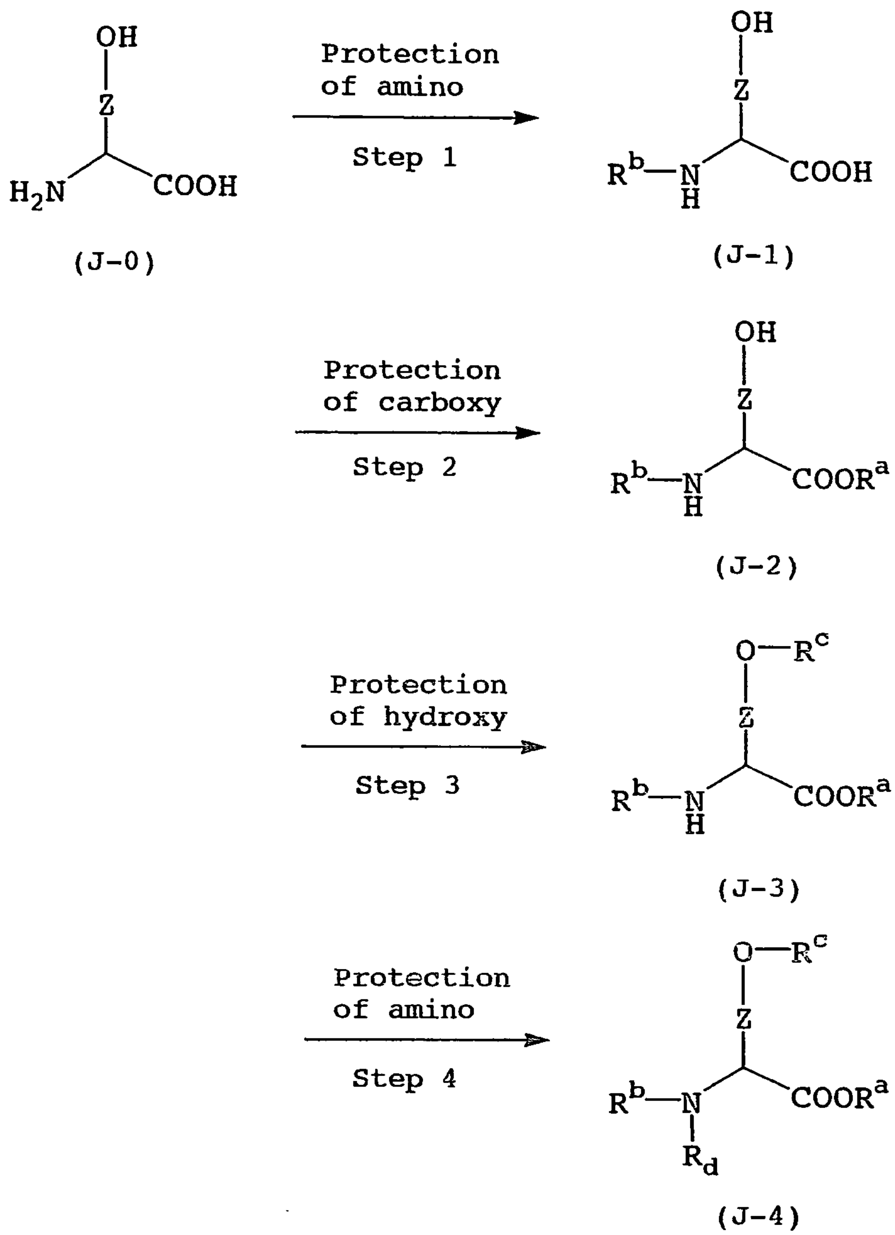
[II-8]

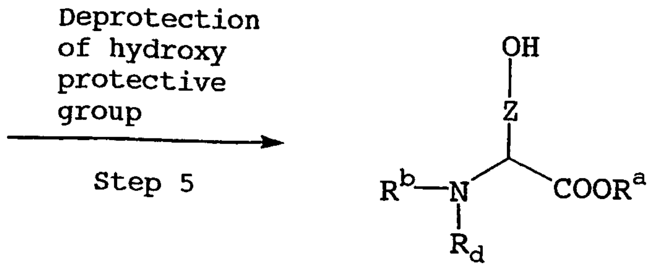
Process I



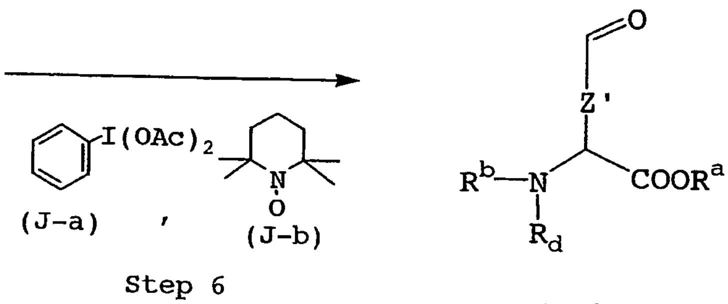
[II-9]

Process J

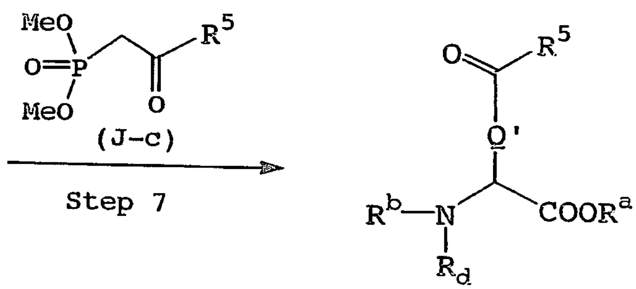

(J-0)
Protection of amino
Step 1
(J-1)
Protection of carboxy
Step 2
(J-2)
Protection of hydroxy
Step 3
(J-3)
Protection of amino
Step 4
(J-4)


Deprotection of hydroxy protective group
Step 5

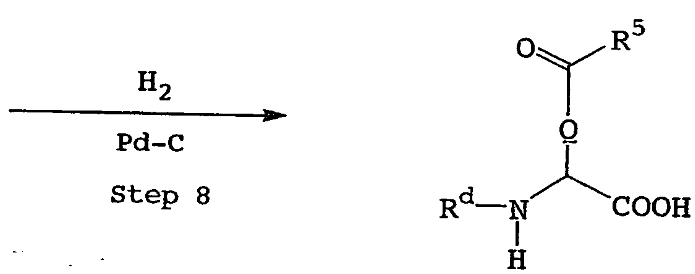
(J-5)


(J-a)
(J-b)
Step 6

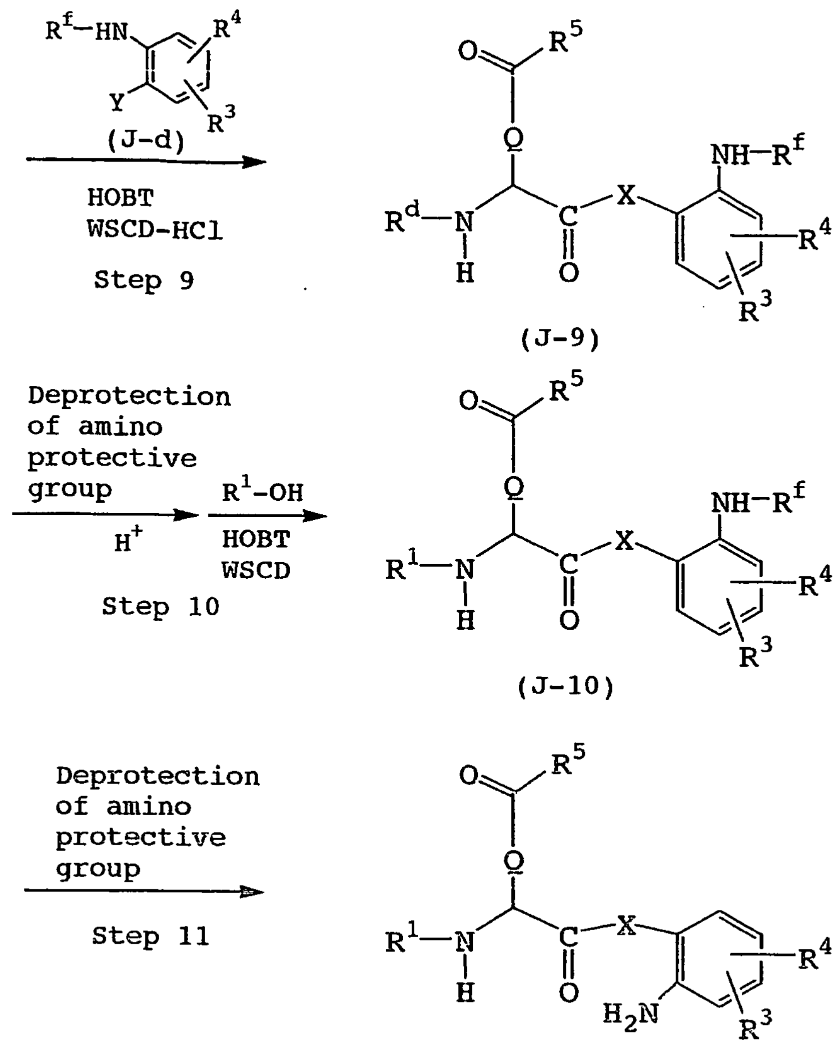
(J-6)


(J-c)
Step 7

(J-7)

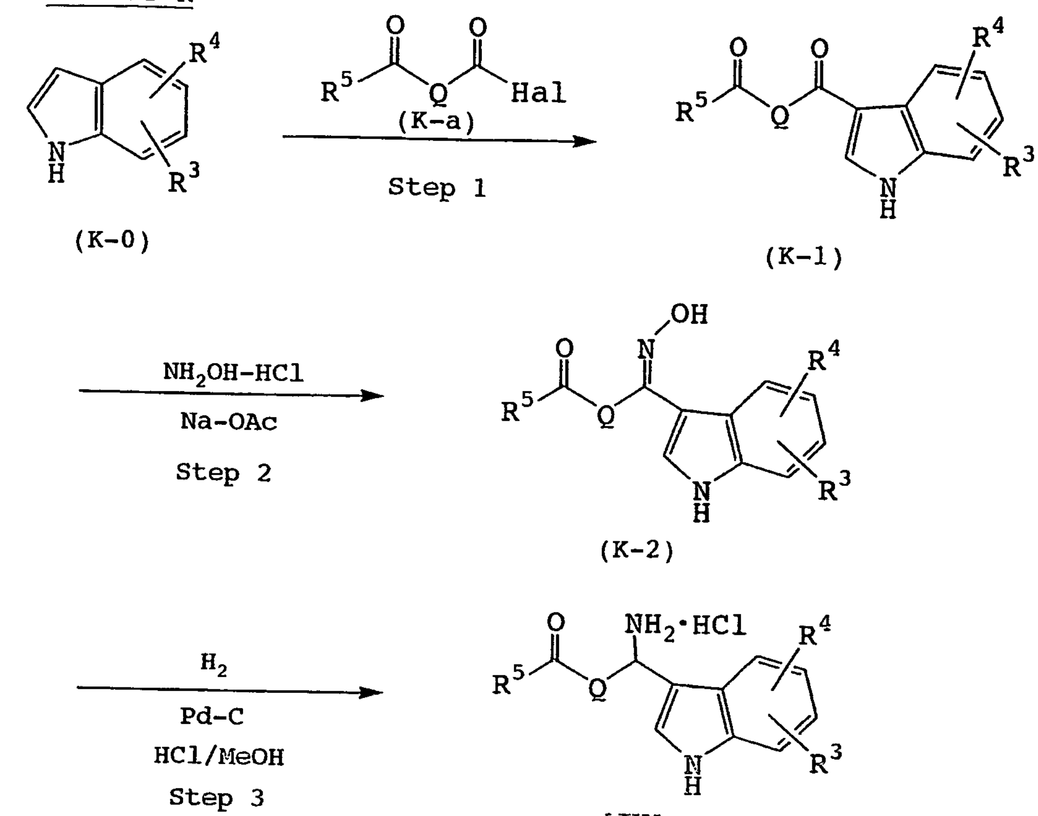

H2
Pd-C
Step 8

(J-8)


(J-d)
HOBT
WSCD-HCl
Step 9
(J-9)
Deprotection of amino protective group
H+
R1-OH
HOBT
WSCD
Step 10
(J-10)
Deprotection of amino protective group
Step 11

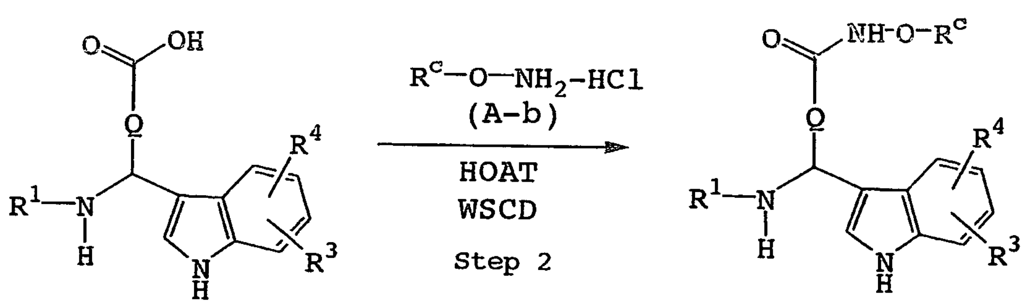
[III-1]

Process K



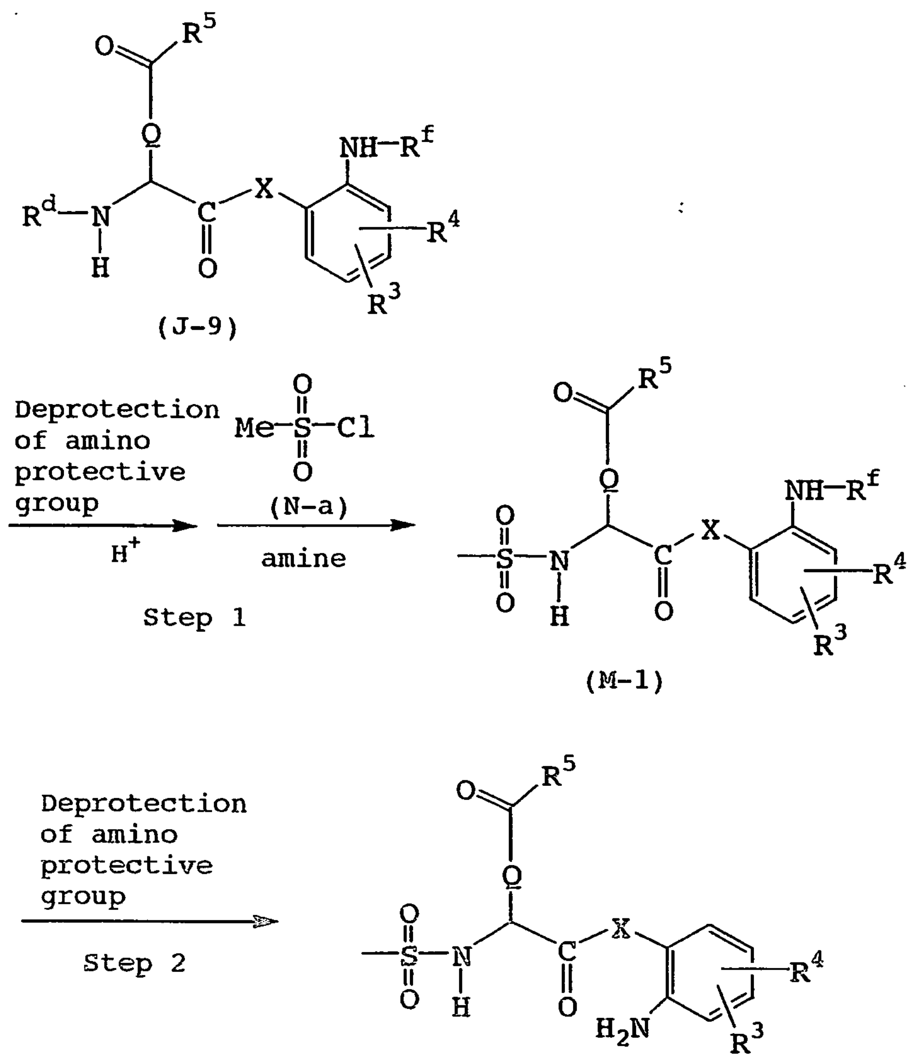
(K-0) (K-1) (K-2) [IV]

Process L



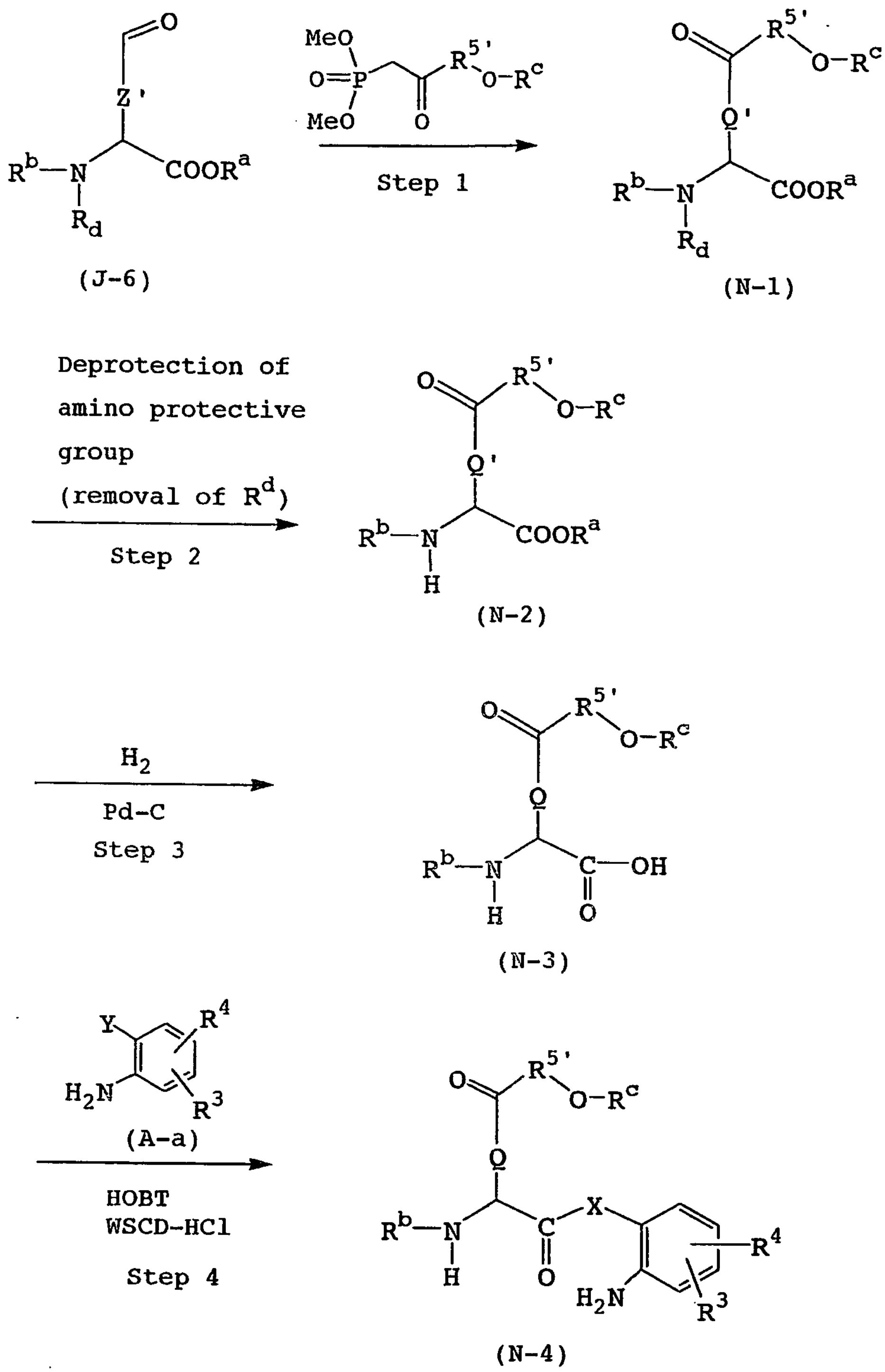
[I-4] [II-10]

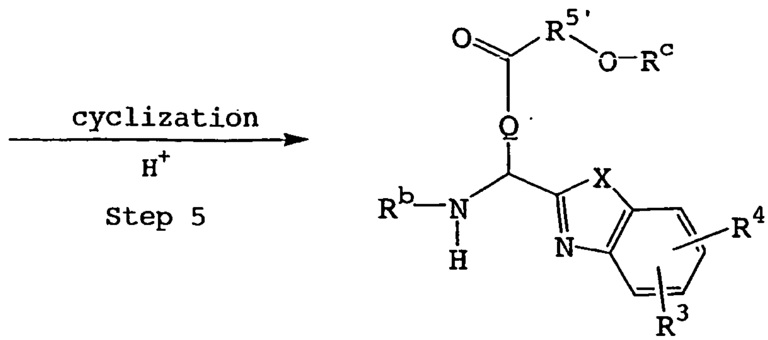
Process M



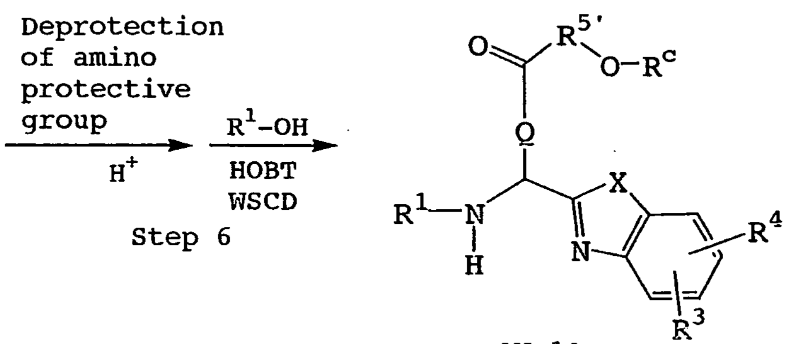
(J-9) (M-1) [III-2]

Process N


(J-6)
Step 1
(N-1)
Deprotection of amino protective group (removal of R^d)
Step 2
(N-2)
H2
Pd-C
Step 3
(N-3)
(A-a)
HOBT
WSCD-HCl
Step 4
(N-4)

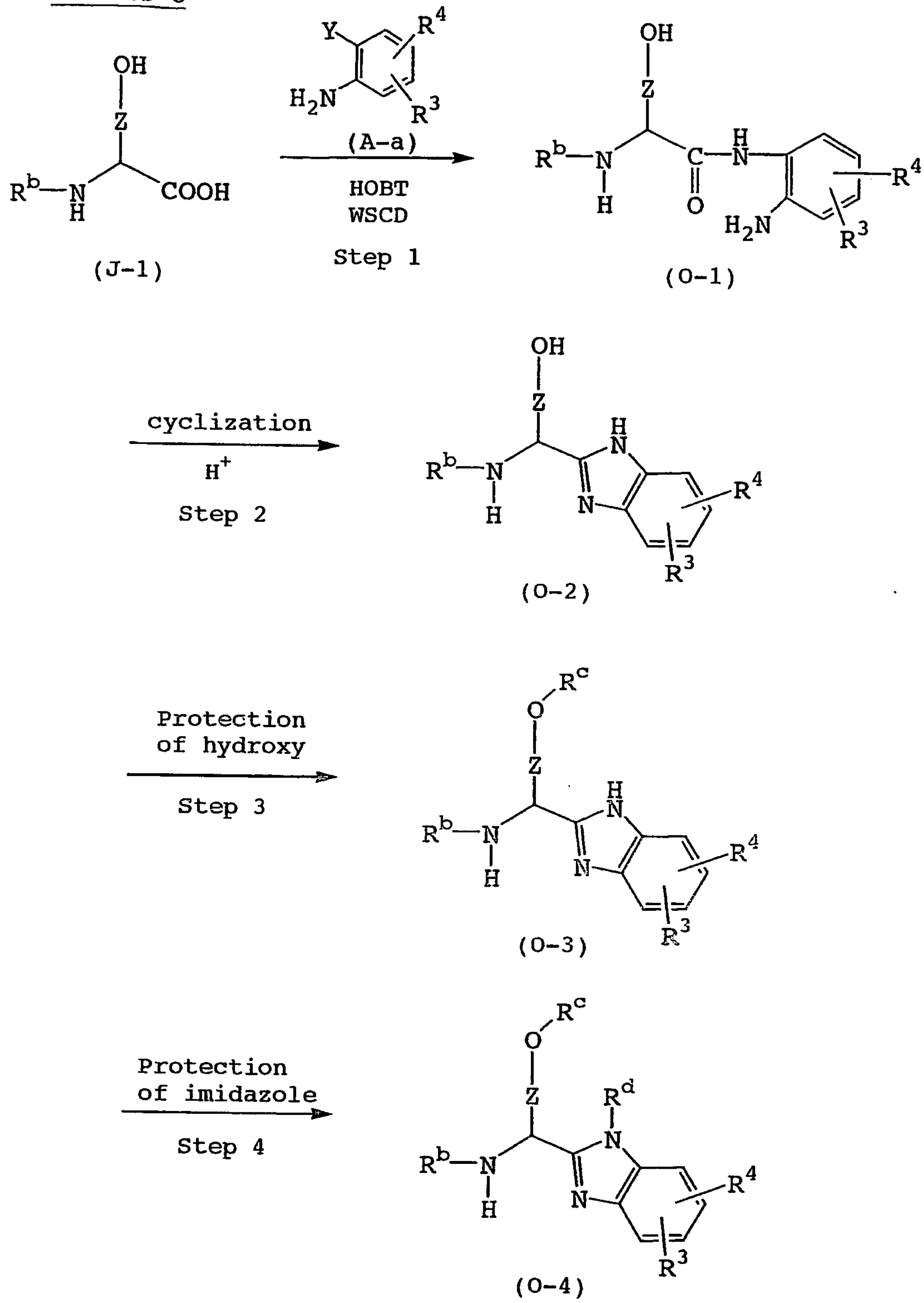


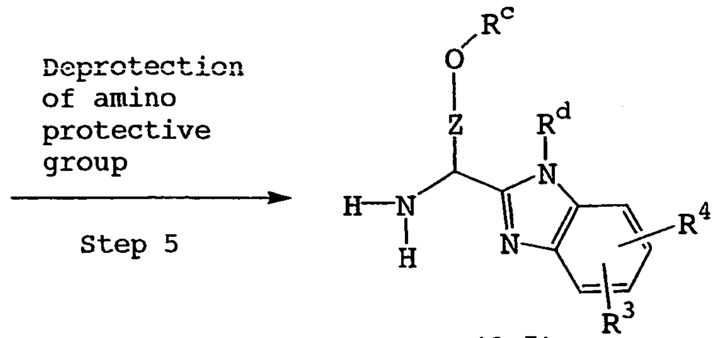
(N-5)



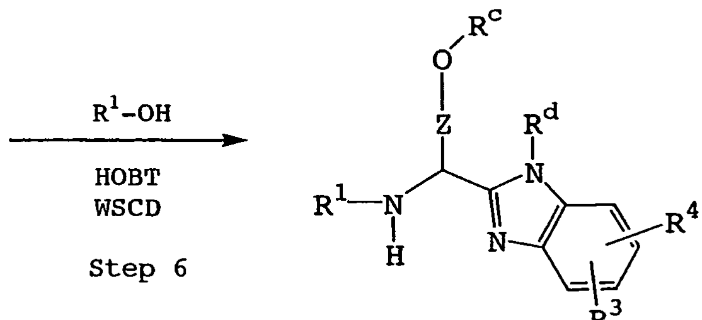
[V-1]

Process O

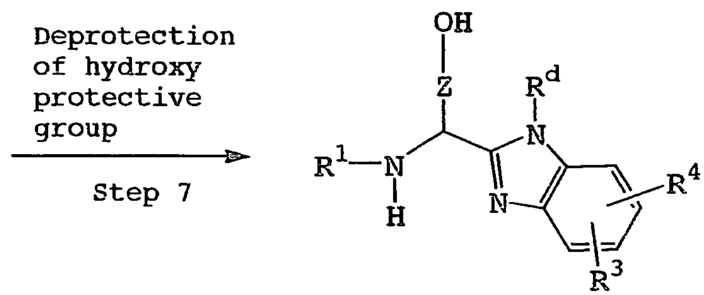

(A-a)
HOBT
WSCD
Step 1
(J-1)
(O-1)
cyclization
H^+
Step 2
(O-2)
Protection of hydroxy
Step 3
(O-3)
Protection of imidazole
Step 4
(O-4)


Deprotection
of amino
protective
group
Step 5

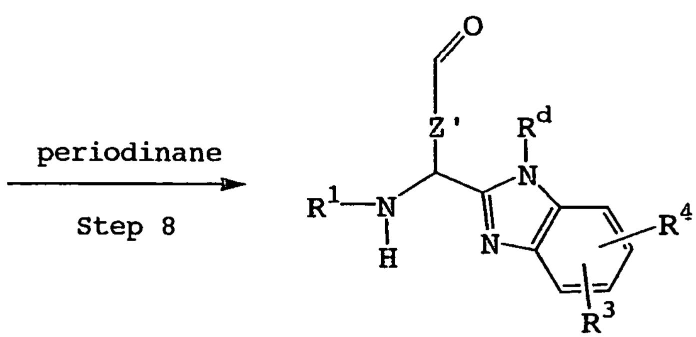
(O-5)


R^1-OH
HOBT
WSCD
Step 6

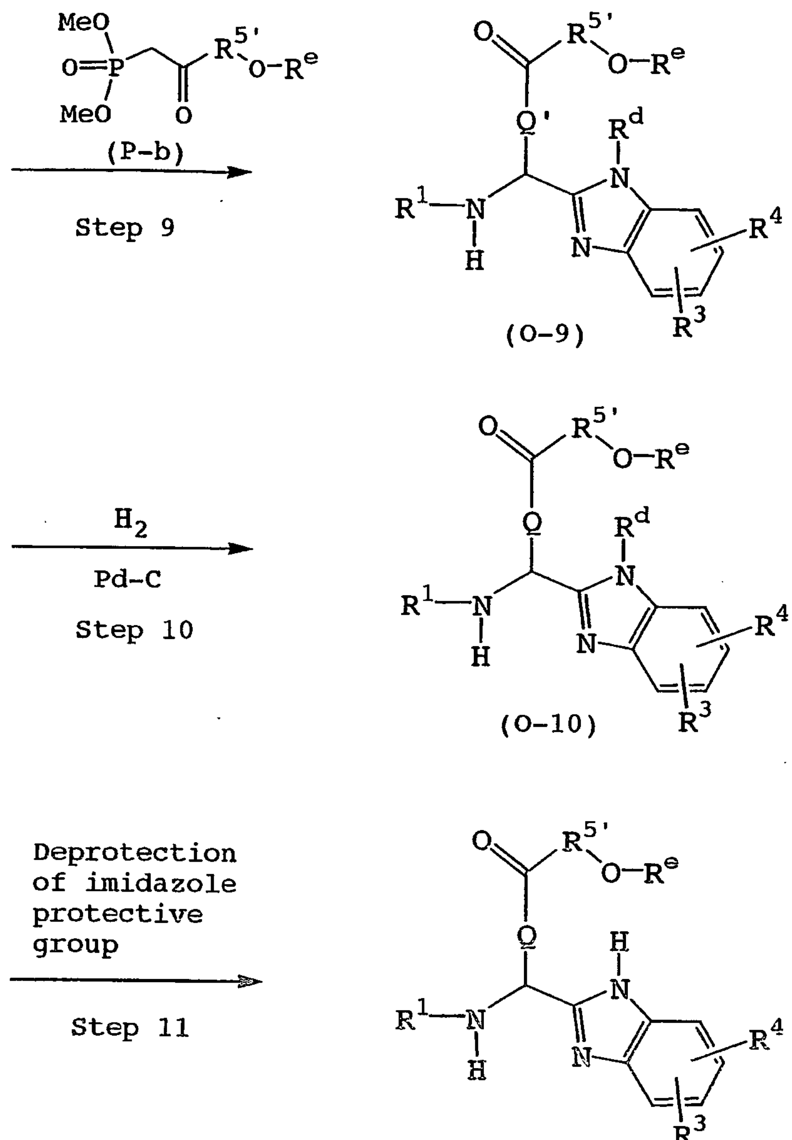
(O-6)


Deprotection
of hydroxy
protective
group
Step 7

(O-7)


periodinane
Step 8

(O-8)

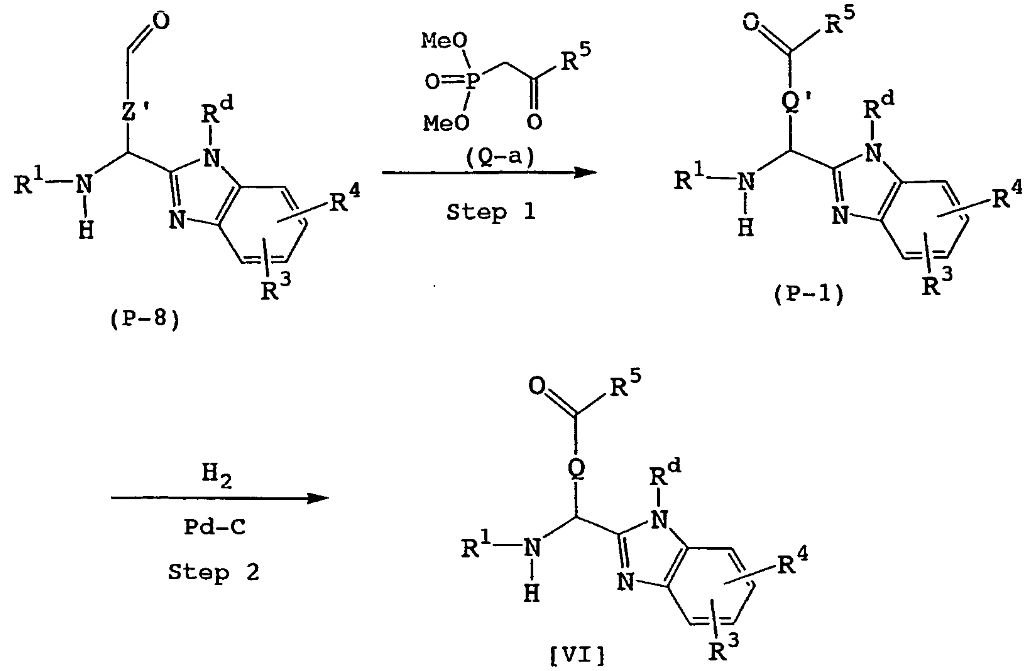

(P-b)
Step 9
H_2
Pd-C
Step 10
Deprotection of imidazole protective group
Step 11

(O-9)

(O-10)

[V-2]

Process P



wherein

R^1, R^2, R^3, R^4, R^5, Q and X are as defined above,

$R^{5'}$ is lower alkylene such as methylene, methylmethylene, ethylmethylene, ethylene, propylene and the like,

R^6 is a group such as lower alkyl (e.g., methyl, ethyl, propyl and the like), aryl (e.g., phenyl, benzyl and the like) and the like,

R^7 is a group such as lower alkyl (e.g., methyl, ethyl, propyl and the like) and the like,

R^8 is a group such as lower alkyl (e.g., ethyl, propyl, butyl and the like), aryl (e.g., optionally substituted phenyl and the like) and the like,

R^9 is a group such as lower alkyl (e.g., isopropyl, butyl and the like), lower alkoxy (e.g., ethoxy, isobutoxy and the like), lower alkoxycarbonyl(lower)alkyl (e.g., ethoxycarbonylmethyl and the like), optionally substituted amino (e.g., N,N-dimethylamino and the like), optionally substituted aryl (e.g., 3-methylphenyl and the like) and the like,

R^{10} is lower alkyl such as methyl, ethyl, propyl, tert-butyl and the like,

Y is amino, thiol or hydroxy,

w is an integer of 2 to 6,

Z is alkylene represented by the formula $-(CH_2)_m-$,

Z' is alkylene represented by the formula $-(CH_2)_{(m-1)}-$,

(wherein m is an integer of 1 to 6),

Q' is alkenylene group,

R^a is carboxy protective group,

R^c and R^e are each hydroxy protective group, and

R^b, R^d and R^f are each amino protective group.

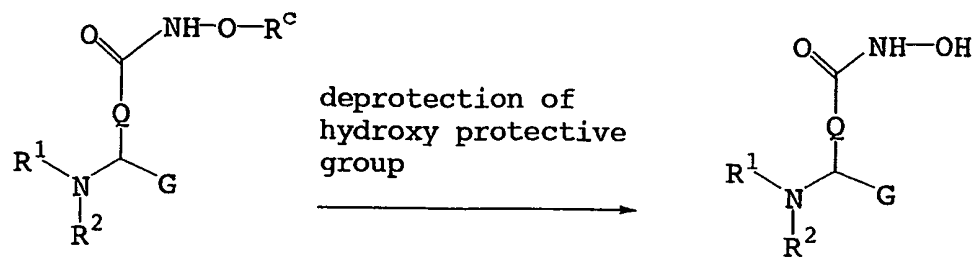
In the above-mentioned Processes A, B, C, D, E, F, G, H, I, J, K, L, M, N, O and P, each of the starting compounds can be prepared, for example, according to the procedures as illustrated in Preparations in the present specification or in a manner similar thereto. For example, the compounds (A-1), (A-2), (A-3), (A-4), (A-5) and (A-6) can be obtained by the procedures as

illustrated in Preparations 1, 2, 3, 4, 5 and 6, respectively; the compound (C-1) can be obtained by the procedure as illustrated in Preparation 23; and the compounds (G-1), (G-2), (G-3), (G-4), (G-5), (G-6), (G-7) and (G-9) can be obtained by the procedures as illustrated in Preparations 77, 78, 79, 80, 81, 82, 83, 84, 85, 86 and 87; and the compound (J-1), (J-2), (J-3), (J-4), (J-5), (J-6), (J-7), (J-8), (J-9), and (J-10) can be obtained by the procedures as illustrated in Preparations 94, 95, 96, 97, 98, 99, 100, 101, 102 and 103; and the compound (K-1) and (K-2), can be obtained by the procedures as illustrated in Preparations 105 and 106; and the compound (M-1) can be obtained by the procedures as illustrated in Preparation 109; and the compound (N-1), (N-2), (N-3), (N-4) and (N-5) can be obtained by the procedures as illustrated in Preparations 111, 112, 113, 114, and 115; and the compounds (O-1), (O-2), (O-3), (O-4), (O-5), (O-6), (O-7), (O-8), (O-9) and (O-10) can be obtained by the procedures as illustrated in Preparations 118, 119, 120, 121, 122, 124, 126, 128, 130 and 135; the compound (P-1) can be obtained by the procedures as illustrated in Preparation 133, respectively. The compounds [II-1], [II-2], [II-3], [II-4], [II-5], [II-6], [II-7], [II-8], [II-9] and [II-10] can be obtained by, for example, the procedures as illustrated in Preparations 7, 9, 24, 44, 45, 48, 86, 72, 76 and 108, respectively. The compounds [III-1], [III-2], [IV], [V-1], [V-2] and [VI] can be obtained by, for example, the procedures as illustrated in Preparations 104, 110, 107, 116, 140 and 138,respectively.

The compound [I] of the present invention is obtained from compound [II] according to, for example, the following process.

Preparation of the compound [I] of the present invention

Process 1



[II] [I-1]

wherein

R^1, R^2, R^3, R^4, R^c, Q and X are as defined above.

The compound [I-1] is obtained by deprotecting the hydroxy protective group of the compound [II]

The reaction may be carried out in the presence of a catalyst for hydrogenation and under the atmosphere of hydrogen.

Suitable catalysts for the hydrogenation include, for example, palladium-$BaSO_4$ (Pd-$BaSO_4$), palladium on carbon (Pd-C), $Pd(OH)_2$ on carbon and the like.

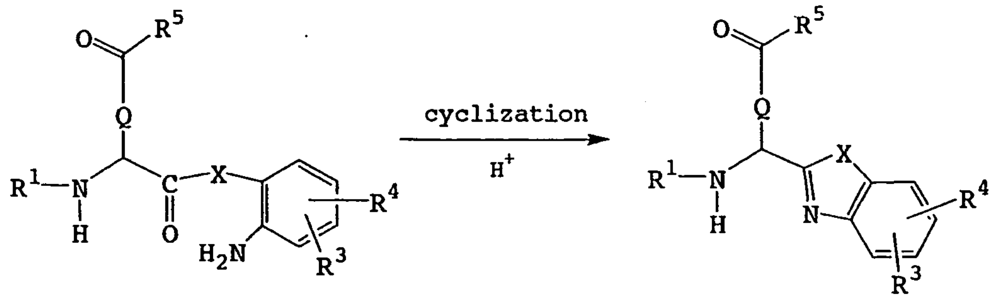
Alternatively, when the hydroxy protective group is hydroxypyranyl, the deprotection of the hydroxy group is carried out in the presence of an acid. Suitable acids include, for example, hydrochloric acid and the like.

The deprotection may be carried out in a conventional solvent which does not adversely influence the reaction, which is exemplified by methanol, ethyl acetate, ethanol, 1,4-dioxane and the like.

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

The Process 1 is exemplified by, for example, Examples 1, 8 and the like.

Process 2



[III] [I-2]

wherein

R^1, R^3, R^4, R^5, Q and X are as defined above.

The compound [I-2] is obtained by cyclization of the compound [III].

In this reaction, the compound [III] includes the compounds [III-1] and [III-2].

The reaction may be carried out in the presence of a catalyst for cyclization.

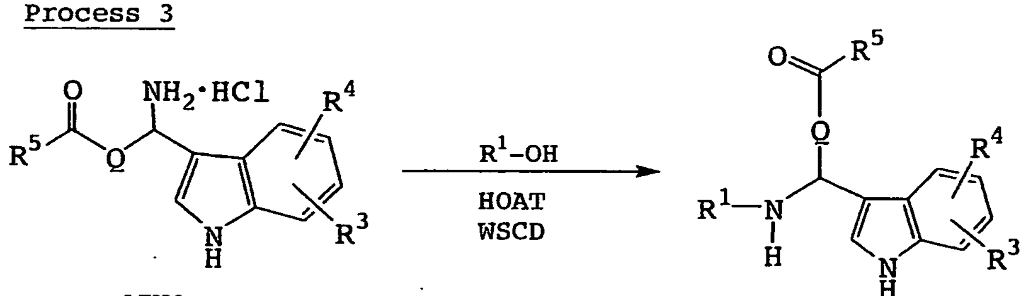
Suitable catalysts for the cyclization include, for example, acids such as hydrochloric acid, acetic acid and the like.

The cyclization may be carried out in a conventional solvent which does not adversely influence the reaction, which is exemplified by methanol, ethanol and the like.

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

The Process 2 is exemplified by Examples 53 and 57.

Process 3



[IV] [I-3]

wherein

R^1, R^3, R^4, R^5,and Q are as defined above.

The compound [I-3] is obtained by reaction of the compound

[IV] with R^1-OH.

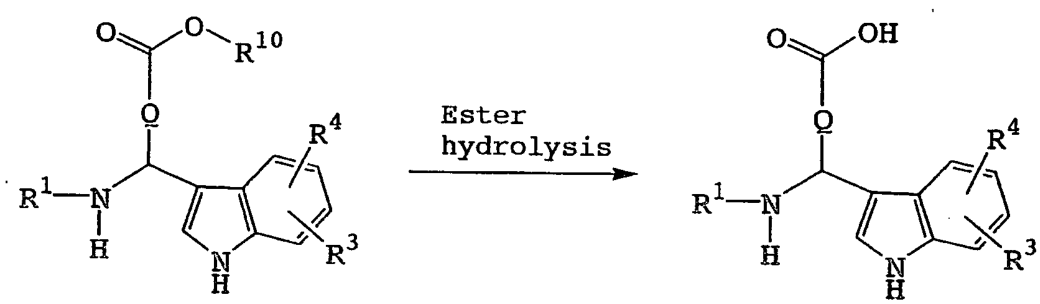
The reaction may be carried out, for example, in the presence of reagents such as HOAT, HOBT, WSCD and the like.

The reaction may be carried out in a conventional solvent which does not adversely influence the reaction, which is exemplified by N,N-dimethylformamide, dichloromethane and the like.

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

The Process 3 is exemplified by Example 54.

Process 4



[I-3'] [I-4]

wherein

R^1, R^3, R^4, R^{10}, and Q are as defined above.

The compound [I-4] is obtained by deprotecting the hydroxy protective group of the compound [I-3'].

In this reaction, the compound [I-3'] is the compound [I-3] wherein R^5 is lower alkoxy represented by the formula $-OR^{10}$ (wherein R^{10} is lower alkyl such as methyl, ethyl, propyl, tert-butyl and the like).

The reaction may be carried out by heating in the presence of water and a catalyst for ester hydrolysis.

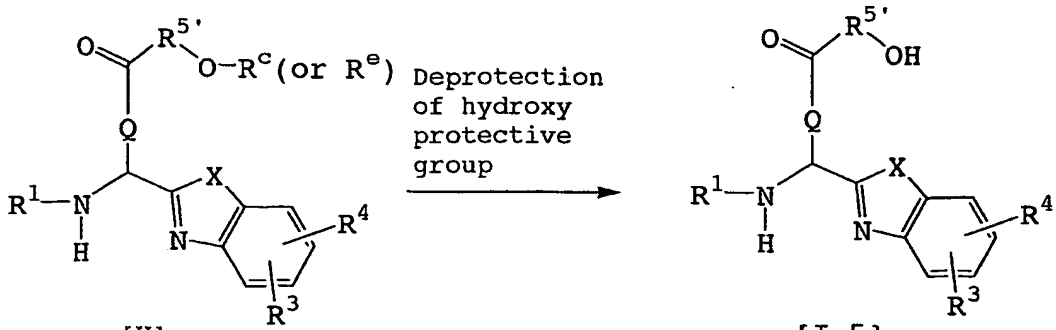
Suitable catalysts for the ester hydrolysis include, for example, bases such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like.

The ester hydrolysis may be carried out in a conventional solvent which does not adversely influence the reaction, which is exemplified by methanol, ethanol and the like.

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

The Process 4 is exemplified by Example 55.

Process 5



[V] [I-5]

wherein

R^1, R^3, R^4, $R^{5'}$, R^c, R^e, Q and X are as defined above.

The compound [I-5] is obtained by deprotecting the hydroxy protective group of the compound [V].

The deprotection reaction may be carried out in the presence of a catalyst for elimination reaction of trisubstituted silyl group.

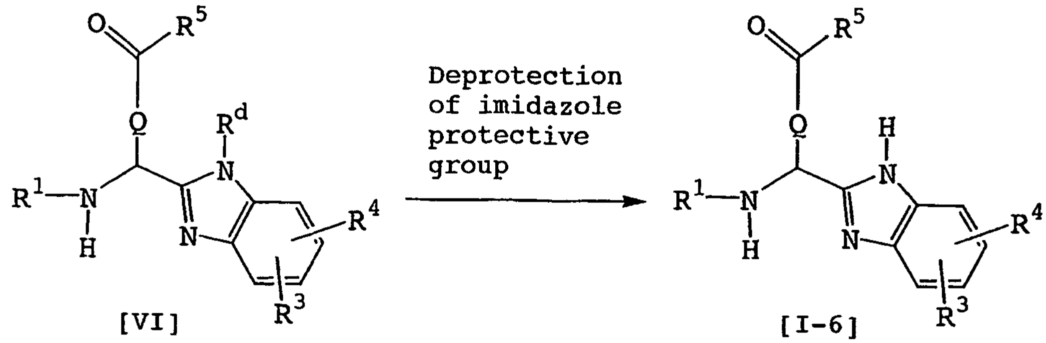
Suitable catalysts for the elimination reaction include, for example, catalysts such as tetrabutylammonium fluoride, hydrogen fluoride, hydrogen fluoride-pyridine complex, acetic acid, hydrochloric acid, sodium hydroxide and the like.

The deprotection may be carried out in a conventional solvent which does not adversely influence the reaction, which is exemplified by ether such as tetrahydrofuran and the like.

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

The Process 5 is exemplified by Example 58.

Process 6



wherein

R^1, R^3, R^4, R^5, R^d and Q are as defined above.

The compound [I-6] is obtained by deprotecting the imidazole protective group of the compound [VI]

The reaction may be carried out in the presence of a catalyst for deprotection reaction of imidazole deprotective group.

Suitable catalysts for the deprotection reaction include, for example, diammonium cerium nitrate, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and the like.

The deprotection may be carried out in a conventional solvent which does not adversely influence the reaction, which is exemplified by dichloromethane, mixed solvent of acetonitrile, methanol and water, and the like.

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

The Process 6 is exemplified by Example 60.

When the compound [I] has stereoisomers, such isomers are also encompassed in the present invention.

The compound [I] may form a salt, which is also encompassed in the present invention. For example, when a basic group such as an amino group is present in a molecule, the salt is exemplified by an acid addition salt (e.g., a salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid and the like, a salt with an organic acid such as methanesulfonic acid, fumaric acid, maleic acid, mandelic acid, citric acid, salicylic acid and the like), and when an acidic

group such as carboxyl group is present, the salt is exemplified by a basic salt (e.g., a salt with a metal such as sodium, potassium, calcium, magnesium, aluminium and the like, a salt with an amino acid such as lysine and the like) and the like.

In addition, solvates of the compound [I] such as hydrate, ethanolate and the like, are also encompassed in the present invention.

Suitable examples and illustration of the various definitions in the above and subsequent descriptions, which the present invention intends to include within its scope, are explained in detail as follows:

Each of the "halogen", "halo" and "Hal" includes fluorine, chlorine, bromine and iodine.

The "lower" used in the description is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

The "one or more" as used herein mean the number of 1 to 6, preferably 1 to 3.

Suitable examples of the "lower alkyl" include a straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, neopentyl, hexyl, isohexyl and the like. Suitable "lower alkyl" as substituents of the "arylcarbonyl" for R^1 includes methyl, isopropyl and the like. Suitable examples of the "lower alkyl" for R^5 include ethyl and the like.

Suitable examples of the "lower alkoxy" include a straight or branched one having 1 to 6 carbon atom(s), such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, tert-pentyloxy, neopentyloxy, hexyloxy, isohexyloxy and the like. Suitable examples of the "lower alkoxy" as substituents of the "aryl(lower)alkyl" for R^3 and/or R^4 include methoxy and the like. Suitable examples of the "lower alkoxy" for R^5 include ethoxy and the like.

Suitable examples of the "aryl" include a C_6-C_{16} aryl such as phenyl, naphthyl, anthryl, pyrenyl, phenanthryl, azulenyl and the like. Suitable examples of the "aryl" for R^3 and/or R^4

include phenyl and the like.

Suitable examples of the "halo(lower)alkyl" include a lower alkyl substituted with 1 to 3 halogen atom(s), such as monochloromethyl, dichloromethyl, trichloromethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, monobromomethyl, dibromomethyl, tribromomethyl, monochloroethyl, dichloroethyl, trichloroethyl, monofluoroethyl, difluoroethyl, trifluoroethyl and the like. Suitable examples of the "halo(lower)alkyl" for R^3 and/or R^4 include, such as trifluoromethyl and the like, and suitable examples of the "halo(lower)alkyl" for R^5 include fluoromethyl, difluoromethyl and the like.

Suitable examples of the "hydroxy(lower)alkyl" include a lower alkyl substituted with hydroxy, such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxymethyl, 1-hydroxypropyl, 2-hydroxypropyl, 1-hydroxybutyl, 1-hydroxypentyl, 1-hydroxyhexyl and the like. Suitable examples of the "hydroxy(lower)alkyl" for R^5 include hydroxymethyl, 1-hydroxyethyl, 1-hydroxypropyl and the like.

The "acyl" as used herein includes, for example,
alkanoyl [e.g., formyl, lower alkyl-carbonyl (e.g., acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, pivaloyl, 2,2-dimethylpropanoyl, hexanoyl and the like), heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl and the like];
alkoxycarbonyl [e.g., lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl and the like) and the like];
lower alkyl-carbonyloxy(lower)alkylcarbonyl (e.g. acetyloxyacetyl, ethylcarbonyloxyacetyl and the like);
arylcarbonyl [e.g., C_{6-10} arylcarbonyl (e.g., benzoyl, toluoyl, naphthoyl, fluorenylcarbonyl and the like)];
arylalkanoyl [e.g., phenyl(lower)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl,

phenylpentanoyl, phenylhexanoyl and the like), naphthyl(lower)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl and the like) and the like];

arylalkenoyl [e.g., aryl(C_3-C_6)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl and the like) and the like)];

naphthylalkenoyl [e.g., naphthyl(C_3-C_6)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, naphthylmethacryloyl, naphthylpentenoyl, naphthylhexenoyl and the like) and the like];

arylalkoxycarbonyl [e.g., aryl(lower)alkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl and the like), fluorenyl(lower)alkoxycarbonyl (e.g., fluorenylmethyloxycarbonyl and the like) and the like];

aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl and the like);

aryloxyalkanoyl [e.g., aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl and the like) and the like];

heterocyclic acyl (e.g., heterocycliccarbonyl and the like);

heterocyclicalkanoyl [e.g., heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl and the like) and the like]; heterocyclicalkenoyl [e.g., heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl and the like)];

carbamoyl;

alkylcarbamoyl [e.g., lower alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl and the like)];

alkoxycarbamoyl [e.g., lower alkoxycarbamoyl (e.g., methoxycarbamoyl, ethoxycarbamoyl and the like)] and the like;

arylcarbamoyl [e.g., C_{6-10} arylcarbamoyl (e.g., phenylcarbamoyl, naphthylcarbamoyl and the like) and the like];

arylthiocarbamoyl [e.g., C_{6-10} arylthiocarbamoyl (e.g., phenylthiocarbamoyl, naphthylthiocarbamoyl and the like) and the like];

alkylsulfonyl [e.g., lower alkylsulfonyl (e.g., methylsulfonyl,

ethylsulfonyl and the like)];

alkoxysulfonyl [e.g., lower alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl and the like)] and the like;

arylsulfonyl (e.g., phenylsulfonyl and the like);

arylglyoxyloyl [e.g., C_{6-10} arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl and the like) and the like];

heterocyclicglyoxyloyl; and the like. Each of these acyl is optionally substituted by one or more suitable substituent(s).

Suitable "acyl" for R^1 is as follows:

(1) arylcarbonyl in which the aryl portion is optionally substituted with one or more suitable substituent(s);

(2) heterocyclic carbonyl;

(3) lower alkyl-carbonyl;

(4) carbamoyl in which the amino portion is optionally mono- or di-substituted with suitable substituent(s);

(5) lower alkyl-carbonyloxy(lower)alkylcarbonyl;

(6) lower alkoxycarbonyl;

(7) lower alkylsulfonyl;

(8) arylsulfonyl and the like.

The "lower alkyl" in each of the "(3) lower alkyl-carbonyl", "(5) lower alkyl-carbonyloxy(lower)alkylcarbonyl" and "(7) lower alkylsulfonyl" has the same meaning as that of the above-mentioned "lower alkyl". Suitable examples of the "(3) lower alkyl-carbonyl" include acetyl, n-butylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl, n-hexylcarbonyl and the like. Suitable examples of the "(5) lower alkyl-carbonyloxy(lower)alkylcarbonyl" include acetyloxyacetyl, ethylcarbonyloxyacetyl and the like. Suitable examples of the "(7) lower alkylsulfonyl" for R^1 include methylsulfonyl and the like.

The "lower alkoxy" in the "(6) lower alkoxycarbonyl" has the same meaning as that of the above-mentioned "lower alkoxy". Suitable examples of the "(6) lower alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl and the like.

The "aryl" in the "(1) arylcarbonyl in which the aryl portion is optionally substituted with one or more suitable

substituent(s)" has the same meaning as that of the above-mentioned "aryl". Suitable examples of the "arylcarbonyl" include benzoyl, naphthoyl and the like. Preferably, the "(1) arylcarbonyl in which the aryl portion is optionally substituted with one or more suitable substituent(s)" is benzoyl in which the phenyl portion is optionally substituted with one or more substituent(s) selected from the group consisting of lower alkoxycarbonyl (e.g., methoxycarbonyl and the like); carboxy; lower alkylcarbamoyl (e.g., methylcarbamoyl and the like); N,N-di(lower)alkylamino (e.g., N,N-dimethylamino and the like); lower alkyl (e.g., methyl, isopropyl and the like); hydroxy; and cyano.

The "aryl" in the "(8) arylsulfonyl" has the same meaning as that of the above-mentioned "aryl". Suitable examples of the "(8) arylsulfonyl" include phenylsulfonyl and the like.

Suitable "heterocyclic" as used herein includes a 5- or 6-membered heteromonocyclic group or a condensed heterocyclic group, each of which contains at least one heteroatom selected from a sulfur atom, an oxygen atom and a nitrogen atom besides carbon atoms and one or more carbon atom(s) is/are optionally replaced with oxo group(s).

Suitable examples of the "heteromonocyclic group" include pyridyl, dihydropyridyl, azepinyl (e.g., 1H-azepinyl and the like), pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl and the like), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl and the like), perhydroazepinyl (e.g., perhydro-1H-azepinyl and the like), pyrrolidinyl, imidazolidinyl, piperidyl, piperadinyl, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl and the like), morpholinyl, sydnonyl, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiazidiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl and the like), dihydrothiazinyl, thiazolidinyl, furyl, dihydrooxatiinyl, N-succinimidyl and the like.

Suitable examples of the "condensed heterocyclic group"

include indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, quinoxalinyl, imidazopyridyl (e.g., imidazo[4,5-c]pyridyl and the like), tetrahydroimidazopyridyl (e.g., 4,5,6,7-tetrahydro[4,5-c]pyridyl and the like), 7-azabicyclo[2.2.1]heptyl, 3-azabicyclo[3.2.2]nonanyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzothienyl, benzodithiinyl, benzoxathiinyl and the like.

Suitable "heterocyclic ring" for R^1 and R^2 include N-succinimidyl and the like.

Suitable "(2) heterocyclic carbonyl" include pyridylcarbonyl, pyradinylcarbonyl, furylcarbonyl, indolylcarbonyl and the like.

Suitable examples of the "(4) carbamoyl in which the amino portion is optionall mono- or di- substituted with suitable substituent(s)" include N,N-dimethylcarbamoyl and the like.

Suitable examples of the "aryl(lower)alkyl" include a phenyl(C_1-C_6)alkyl such as benzyl, phenethyl, phenylpropyl, phenylbutyl, phenylhexyl and the like, a naphthyl(C_1-C_6)alkyl such as naphthylmethyl, naphthylethyl, naphthylpropyl, naphthylbutyl, naphthylpentyl, naphtylhexyl and the like. Suitable examples of the "aryl(lower)alkyl optionally substituted with one or more suitable substituent(s)" for R^3 and/or R^4 include an aryl(lower)alkyl in which the alkyl portion is optionally substutituted with one or more substituent(s) such as hydroxy, lower alkoxy (e.g., methoxy, ethoxy) and the like, such as (hydroxyphenyl)methyl, (methoxyphenyl)methyl and the like.

Suitable examples of the "aromatic ring" for R^3 and R^4 include benzene ring and the like.

Suitable examples of the "lower alkylene" include a straight or branched alkylene having 1 to 6 carbon atom(s), such as ethylene, propylene, 1-methylpropylene, butylene, 1-methylbutylene, 2-methylbutylene, 1-ethylbutylene, 2-ethylbutylene, pentylene, 1-methylpentylene, 2-methylpentylene, hexylene and the like. Suitable examples of the "lower alkylene"

for Q include pentylene and the like.

Suitable examples of the "lower alkenylene" include a straight or branched alkenylene having 1 to 6 carbon atom(s), such as vinylene, 1-methylvinylene, 2-methylvinylene, 1-propenylene, 2-propenylene, 2-methyl-1-propenylene, 2-methyl-2-propenylene, 1-butenylene, 2-butenylene, 3-butenylene, 1-pentenylene, 2-pentenylene, 3-pentenylene, 4-pentenylene, 1-hexenylene, 2-hexenylene, 3-hexenylene, 4-hexenylene, 5-hexenylene and the like. Suitable examples of the "lower alkenylene" for Q include 1-pentenylene and the like.

Suitable examples of the "carboxy protective group" include:

lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl and the like);

mono(or di or tri)halo(lower)alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl and the like), preferably 2,2,2-trichloroethyl;

lower alkanoyloxy(lower)alkyl (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, valeryloxymethyl, pivaloyloxymethyl, hexanoyloxymethyl, 1(or 2)-acetoxyethyl, 1(or 2 or 3)-acetoxypropyl, 1(or 2 or 3 or 4)-acetoxybutyl, 1(or 2)-propionyloxyethyl, 1(or 2 or 3)-propionyloxypropyl, 1(or 2)-butyryloxyethyl, 1(or 2)-isobutyryloxyethyl, 1(or 2)-pivaloyloxyethyl, 1(or 2)-hexanoyloxyethyl, isobutyryloxymethyl, 2-ethylbutyryloxymethyl, 3,3-dimethylbutyryloxymethyl, 1(or 2)-pentanoyloxyethyl and the like);

lower alkanesulfonyl(lower)alkyl (e.g. 2-mesylethyl and the like);

lower alkoxycarbonyloxy(lower)alkyl (e.g. methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, 2-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl, 1-isopropoxycarbonyloxyethyl and the like);

[5-(lower)alkyl-2-oxo-1,3-dioxol-4-yl](lower)alkyl (e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl, (5-propyl-2-oxo-1,3-dioxol-4-yl)methyl and the like);

aryl optionally substituted with one or more suitable

substituent(s) (e.g. phenyl, o(or m or p)-chlorophenyl, tolyl, o(or m or p)-t-butylphenyl, xylyl, mesityl, cumenyl and the like);

ar(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. benzyl, p-methoxybenzyl, o(or p)-nitrobenzyl, phenethyl, trityl, benzhydryl, bis(methoxyphenyl)methyl, m,p-dimethoxybenzyl, 4-hydroxy-3,5-di-t-butylbenzyl and the like);

arylcarbonyl(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. phenacyl and the like);

cyclo(lower)alkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like);

lower alkenyl (e.g. vinyl, allyl and the like);

lower alkynyl (e.g. ethynyl, propynyl and the like);

trisubstituted silyl such as tri(lower)alkylsilyl (e.g. trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl and the like), lower alkyldiarylsilyl (e.g. methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl, and the like) and the like;

tri(lower)alkylsilyl(lower)alkyl (e.g. 2-(trimethylsilyl)ethyl and the like);

1-(lower)alkyl-2,6,7-trioxabicyclo[2.2.2]oct-4-yl (e.g. 1-methyl-2,6,7-trioxabicyclo[2.2.2]oct-4-yl, 1-ethyl-2,6,7-trioxabicyclo[2.2.2]oct-4-yl, and the like); and the like.

Suitable examples of the "hydroxy protective group" include:

lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl and the like);

lower alkoxy(lower)alkyl (e.g., methoxymethyl, 1-ethoxyethyl and the like);

lower alkoxy(lower)alkoxy(lower)alkyl (e.g., 2-methoxyethoxymethyl and the like);

aryl(lower)alkyl in which the aryl portion is optionally

substituted with one or more suitable substituent(s) (e.g., benzyl, p-methoxybenzyl, m,p-dimethoxybenzyl and the like); aryl(lower)alkoxy(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g., benzyloxymethyl, p-methoxybenzyloxymethyl and the like); lower alkylthio(lower)alkyl (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl and the like);
heterocyclic group (e.g., tetrahydropyranyl and the like); trisubstituted silyl [e.g., tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl (TBDMS), tri-tert-butylsilyl and the like), lower alkyldiarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl (TBDPS) and the like) and the like];
acyl as described above;
lower alkenyl (e.g., vinyl, allyl and the like); and the like.

Suitable examples of the "amino protective group" include:
acyl as described above;
aryl(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g., benzyl, p-methoxybenzyl, o(or p)-nitrobenzyl, phenethyl, trityl, benzhydryl, bis(methoxyphenyl)methyl, m,p-dimethoxybenzyl, 4-hydroxy-3,5-di-t-butylbenzyl and the like);
[5-(lower)alkyl-2-oxo-1,3-dioxol-4-yl](lower)alkyl (e.g., (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl, (5-propyl-2-oxo-1,3-dioxol-4-yl)methyl and the like);
and the like.

Suitable examples of the "imidazole protective group" include those exemplified for the "amino protective group" described above and the like.

The following abbreviations are also used in the present specification: Boc (t-butyloxycarbonyl); HOBT (1-hydroxybenzotriazole); WSCD (1-ethyl-3-(3'-dimethylaminopropyl)-

carbodiimide); DMF (N,N-dimethylformamide); aq. (aqueous solution); Me (methyl); MeOH (methanol); Et (ethyl); EtOH (ethanol); tBu (t-butyl); t-Boc (t-butoxycarbonyl); TsCl (p-toluenesulfonyl chloride); Ac (acetyl); AcOH (acetic acid); Ph (phenyl); DIEA (diisopropylethylamine); Bn (benzyl); Bz (benzoyl); TBAI (tetrabutylammonium iodide); TBAF (tetrabutylammonium fluoride); CAN (cerium ammonium nitrate); THP (tetrahydropyranyl); IPE (diisopropyl ether); HOAT (1-hydroxy-7-azabenzotriazole); TBDPS (t-butyl(diphenyl)silyl); TBDMS (t-butyl(dimethyl)silyl).

Test Method

In order to show the usefulness of the compound [I] of the invention, the pharmacological test result of the representative compound of the present invention is shown in the following.

Test 1: Determination of histone deacetylase inhibitory activity

The partial purification of human histone deacetylase, the preparation of [^{3}H] acetyl histones, and the assay for histone deacetylase activity were performed as follows basically according to the method as proposed by Yoshida et al.

Partial purification of human histone deacetylase

The human histone deacetylase was partially purified from human T cell leukemia Jurkat cells. Jurkat cells (5×10^8 cells) were suspended in 40 mL of the HDA buffer consisting of 15 mM potassium phosphate (pH 7.5), 5% glycerol and 0.2 mM EDTA. After homogenization, nuclei were collected by centrifugation (35,000 x g, 10 min) and homogenized in 20 mL of the same buffer supplemented with 1 M $(NH_4)_2SO_4$. The viscous homogenate was sonicated and clarified by centrifugation (35,000 x g, 10 min), and the deacetylase was precipitated by raising the concentration of $(NH_4)_2SO_4$ to 3.5 M. The precipitated protein was dissolved in 10 mL of the HDA buffer and dialyzed against 4 liters of the same buffer. The dialyzate was then loaded onto a DEAE-cellulose (Whatman DE52) column (25 x 85 mm) equilibrated with the same buffer and eluted with 300 mL of a linear gradient (0-0.6 M) of NaCl. A single peak of histone deacetylase activity appeared

between 0.3 and 0.4 M NaCl.

Preparation of [^{3}H] acetyl histone

To obtain [^{3}H] acetyl-labeled histone as the substrate for the histone deacetylase assay, 1 x 10^8 cells of Jurkat in 20 mL of RPMI-1640 medium (supplemented with 10% FBS, penicillin (50 units/mL) and streptomycin (50 μg/mL)) were incubated with 300 MBq [^{3}H] sodium acetate in the presence of 5 mM sodium butyrate for 30 min in 5% CO_2-95% air atmosphere at 37°C in a 75 cm^2 flask, harvested into a centrifuge tube (50 mL), collected by centrifugation at 1000 rpm for 10 min, and washed once with phosphate-buffered saline. The washed cells were suspended in 15 mL of ice-cold lysis buffer (pH 6.5, 10 mM Tris-HCl, 50 mM sodium bisulfite, 1% Triton X-100, 10 mM $MgCl_2$, 8.6% sucrose). After Dounce homogenization (30 stroke), the nuclei were collected by centrifugation at 1000 rpm for 10 min, washed 3 times with 15 mL of the lysis buffer, and once with 15 mL of ice-cooled washing buffer (pH 7.4, 10 mM Tris-HCl, 13 mM EDTA) successively. The pellet was suspended in 6 mL of ice-cooled water using a mixer, and 68 μl of H_2SO_4 was added to the suspension to give a concentration of 0.4 N. After incubation at 4°C for 1 hr, the suspension was centrifuged for 5 min at 15,000 rpm, and the supernatant was taken and mixed with 60 mL of acetone. After overnight incubation at -20°C, the coagulated material was collected by microcentrifugation, air-dried, and stored at -80°C.

Assay for histone deacetylase activity

For the standard assay, 10 μl of [^{3}H] acetyl-labeled histones were added to 90 μl of the enzyme fraction, and the mixture was incubated at 25°C for 30 min. The reaction was stopped by addition of 10 μl of HCl. The released [^{3}H] acetic acid was extracted with 1 mL of ethyl acetate, and 0.9 mL of the solvent layer was taken into 10 mL of toluene scintillation solution for determination of radioactivity.

Test 2: Determination of T-cell growth inhibitor activity

The T lymphocyte blastogenesis test was performed in microtiter plates with each well containing 1.5 x 10^5 splenic

cells of Lewis rats in 0.1 mL RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), 50 mM 2-mercaptoethanol, penicilln (100 units/mL) and streptomycin (100 μg/mL), to which Concanavalin A (1 μg/mL) was added. The cells were incubated at 37°C in a humidified atmosphere of 5% CO_2 for 72 hr. After the culture period, suppressive activities of the test compounds in T lymphocyte blastogenesis were quantified by AlamarBlue (trademark) Assay. The test samples were dissolved in DMSO and further diluted with RPMI-1640 medium and added to the culture. The activities of the test compounds were expressed as IC_{50}.

The results of those tests are shown in the Table 1.

Table 1: HDAC inhibitory activity and T-cell growth inhibitory activity of the compound of the present invention

Examples	Test 1: HDAC inhibitory activity IC_{50} (nM)	Test 2: T-cell growth inhibitory activity IC_{50} (nM)
Compound E1	<10	<4
Compound E3	<10	<4
Compound E4	<10	<4
Compound E5	<10	<4

The pharmaceutical composition of the present invention comprising histone deacetylase inhibitor such as the compound [I] is useful as a therapeutic or prophylactic agent for diseases caused by abnormal gene expression, such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), protozoal infection and the like. Further, it is useful as an antitumor agent or immunosuppressant, which prevents an organ transplant rejection and autoimmune diseases as exemplified

below.

Rejection reactions by transplantation of organs or tissues (e.g., heart, kidney, liver, bone marrow, skin, cornea, lung, pancreas, small intestine, limb, muscle, nerve, intervertebral disc, trachea, myoblast, cartilage and the like) and the like;
graft-versus-host reactions following bone marrow transplantation;
autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes and the like);
infections caused by pathogenic microorganisms (e.g., Aspergillus fumigatus, Fusarium oxysporum, Trichophyton asteroides and the like); and the like.

Furthermore, pharmaceutical preparations of the histone deacetylase inhibitor, such as the compound [I], are useful for the therapy or prophylaxis of the following diseases.

Inflammatory or hyperproliferative skin diseases or cutaneous manifestations of immunologically-mediated diseases (e.g., psoriasis, atopic dermatitis, contact dermatitis, eczematoid dermatitis, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, erythema, dermal eosinophilia, lupus erythematosus, acne, alopecia areata and the like);
autoimmune diseases of the eye (e.g., keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, keratoleukoma, ocular premphigus, Mooren's ulcer, scleritis, Grave's ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy and the like);
reversible obstructive airway diseases [e.g., asthma (e.g., bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, and dust asthma), particularly chronic or inveterate asthma (e.g., late asthma, airway hyper-responsiveness and the

like), bronchitis and the like];

mucosal or vascular inflammations (e.g., gastric ulcer, ischemic or thrombotic vascular injury, ischemic bowel diseases, enteritis, necrotizing enterocolitis, intestinal damages associated with thermal burns, leukotriene B4-mediated diseases and the like);

intestinal inflammations/allergies (e.g., coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis and the like);

food-related allergic diseases with symptomatic manifestation remote from the gastrointestinal tract (e.g., migrain, rhinitis, eczema and the like);

renal diseases (e.g., intestitial nephritis, Goodpasture's syndrome, hemolytic uremic syndrome, diabetic nephropathy and the like);

nervous diseases (e.g., multiple myositis, Guillain-Barre syndrome, Meniere's disease, multiple neuritis, solitary neuritis, cerebral infarction, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), radiculopathy and the like);

cerebral ischemic diseases [e.g., head injury, hemorrhage in brain (e.g., subarachnoid hemorrhage, intracerebral hemorrhage and the like), cerebral thrombosis, cerebral embolism, cardiac arrest, stroke, transient ischemic attack (TIA), hypertensive encephalopathy and the like];

endocrine diseases (e.g., hyperthyroidism, Basedow's disease and the like);

hematic diseases (e.g., pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia and the like);

bone diseases (e.g., osteoporosis and the like);

respiratory diseases (e.g., sarcoidosis, pulmonary fibrosis, idiopathic interstitial pneumonia and the like);

skin diseases (e.g., dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photosensitivity, cutaneous T-cell lymphoma and the like);

circulatory diseases (e.g., arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis and the like);

collagen diseases (e.g., scleroderma, Wegener's granuloma, Sjögren's syndrome and the like);

adiposis;

eosinophilic fasciitis;

periodontal diseases (e.g., damage to gingiva, periodontium, alveolar bone or substantia ossea dentis and the like);

nephrotic syndrome (e.g., glomerulonephritis and the like);

male pattern alopecia, alopecia senile;

muscular dystrophy;

pyoderma and Sezary syndrome;

chromosome abnormality-associated diseases (e.g., Down's syndrome and the like);

Addison's disease;

active oxygen-mediated diseases {e.g., organ injury [e.g., ischemic circulation disorders of organs (e.g., heart, liver, kidney, digestive tract and the like) associated with preservation and transplantation and the like], ischemic diseases (e.g., thrombosis, cardial infarction and the like), intestinal diseases (e.g., endotoxin shock, pseudomembranous colitis, drug- or radiation-induced colitis and the like), renal diseases (e.g., ischemic acute renal insufficiency, chronic renal failure and the like), pulmonary diseases [e.g., toxicosis caused by pulmonary oxygen or drugs (e.g., paracort, bleomycin and the like), lung cancer, pulmonary emphysema and the like], ocular diseases (e.g., cataracta, iron-storage disease (siderosis bulbi), retinitis, pigmentosa, senile plaques, vitreous scarring, corneal alkali burn and the like), dermatitis (e.g., erythema multiforme, linear immunoglobulin A bullous dermatitis, cement dermatitis and the like), other diseases [e.g., gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution (e.g., air pollution and the like), aging, carcinogen, metastasis of carcinoma, hypobaropathy and the like] and the like};

diseases caused by histamine release or leukotriene C4 release; restenosis of coronary artery following angioplasty and prevention of postsurgical adhesions;
autoimmune diseases and inflammatory conditions [e.g., primary mucosal edema, autoimmune atrophic gastritis, premature menopause, male sterility, juvenile diabetes mellitus, pemphigus vulgaris, pemphigoid, sympathetic ophthalmitis, lens-induced uveitis, idiopathic leukopenia, active chronic hepatitis, idiopathic cirrhosis, discoid lupus erythematosus, autoimmune orchitis, arthritis (e.g., arthritis deformans and the like), polychondritis and the like];
Human Immunodeficiency Virus (HIV) infection, AIDS;
allergic conjunctivitis;
hypertrophic cicatrix and keloid due to trauma, burn, surgery and the like; and the like.

Therefore, the pharmaceutical composition of the present invention is useful for the therapy and prophylaxis of liver diseases [e.g., immunogenic diseases (e.g., chronic autoimmune liver diseases such as autoimmune hepatic diseases, primary biliary cirrhosis, sclerosing cholangitis and the like), partial liver resection, acute liver necrosis (e.g., necrosis caused by toxins, viral hepatitis, shock or anoxia and the like), hepatitis B, non-A non-B hepatitis, hepatocirrhosis, hepatic failure (e.g., fulminant hepatitis, late-onset hepatitis and "acute-on-chronic" liver failure (acute liver failure on chronic liver diseases) and the like) and the like].

The pharmaceutical composition of the present invention can be used in the form of pharmaceutical preparation, for example, in a solid, semisolid or liquid form, which contains the histone deacetylase inhibitor, such as the compound [I], as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral administrations. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions,

emulsions, suspensions, injections, ointments, liniments, eye drops, lotion, gel, cream, and any other form suitable for use.

The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in a solid, semisolid, or liquid form. Additionally, auxiliary, stabilizing, thickening, solubilizing and coloring agents and perfumes may be used in combination with the carrier.

For application to human, the composition is preferably applied by intravenous, intramuscular, topical or oral administration, or by a vascular stent impregnated with the compound [I]. While the dosage of therapeutically effective amount of the histone deacetylase inhibitor, such as the compound [I], varies depending upon the age and condition of each individual patient to be treated, when an individual patient is to be treated, in the case of intravenous administration, a daily dose of 0.01-10 mg of the histone deacetylase inhibitor, such as the compound [I], per kg weight of human being, in the case of intramuscular administration, a daily dose of 0.1-10 mg of the histone deacetylase inhibitor, such as the compound of the formula [I], per kg body weight of human being, and in the case of oral administration, a daily dose of 0.5-50 mg of the histone deacetylase inhibitor, such as the compound [I], per kg body weight of human being, is generally given for treatment.

During the preparation of the above-mentioned pharmaceutical administration forms, the compound [I] or a salt thereof can be also combined together with other immunosuppressive substances, such as repamycin, mycophenolic acid, cyclosporin A, tacrolimus and brequinar sodium.

Hereinafter the reactions in respective Preparations and Examples for preparing the compound [I] of the present invention are explained in more detail. The invention should not be restricted by the following Preparations and Examples in any way.

Preparation 1

To a stirred suspension of (2S)-2-amino-8-(benzyloxy)-8-oxooctanoic acid (150 mg) in dioxane (3 mL) were added di-tert-butyldicarbonate (176 mg) in dioxane (1 mL) and 1N-sodium hydroxide (0.8 mL), and the mixture was stirred at ambient temperature for 13 hr. The solvent was evaporated in vacuo. The residue was diluted with water and washed with diethyl ether. The aqueous layer was acidified with 1N-hydrogen chloride to pH 2, and extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo to give Compound (1) as a colorless oil (188 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.28-1.50 (4H, m), 1.45 (3x3H, s), 1.56-1.73 (1H, m), 1.84 (1H, m), 2.36 (2H, t, J=7.3 Hz), 4.28 (1H, m), 4.98 (1H, br-d, J=8 Hz), 5.11 (2H, s), 7.28-7.41 (5H, m);
MASS (ES-): m/e 378.

Preparation 2

To a stirred solution of Compound (1) (182 mg) in N,N-dimethylformamide (4 mL) were added 1-hydroxybenzotriazole (HOBT, 78 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD-HCl, 110 mg) and 1,2-diaminonaphthalene (83.5 mg), and the mixture was stirred at ambient temperature for 18 hr. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogencarbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated in vacuo, and the residue was purified by preparative thin layer chromatography (hexane:ethyl acetate = 1:1) to give Compound (2) as a brown oil (197 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.32-1.54 (4H, m), 1.48 (3x3H, s), 1.57-1.78 (3H, m), 1.96 (1H, m), 2.37 (2H, t, J=7.3 Hz), 4.19 (1H, dt, J=7, 6.5 Hz), 4.43 (2H, br-s), 5.12 (2H, s), 5.12 (1H, m), 7.21-7.50 (9H, m), 7.72-7.81 (2H, m), 7.93 (1H, s);
MASS (ES+): m/e 520.

Preparation 3

A solution of Compound (2) (10.1 g) in a mixed solvent of toluene (108 mL) and acetic acid (12 mL) was stirred at 55°C for 30 min. The solvent was evaporated in vacuo and the residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was separated, washed with brine and dried over sodium sulfate. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (eluting with a mixture of hexane and ethyl acetate=2:1) to give Compound (3) as a brown amorphous (9.75 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.19-1.46 (4H, m), 1.40 (3x3H, s), 1.48-1.62 (2H, m), 1.85 (1H, m), 1.96 (1H, m), 2.35 (2H, t, J=7.3 Hz), 4.82 (1H, m), 5.07 (2H, s), 7.26-7.74 (10H, m), 7.97 (1H, m), 8.38 (1H, m), 12.47 (0.6H, s), 13.00 (0.4H, s);

MASS (ES+): m/e 502.

Preparation 4

A mixture of Compound (3) (282 mg) and 10% palladium on carbon (30 mg) in methanol (6 mL) was stirred under hydrogen atmosphere at ambient temperature for 1 hr. The catalyst was filtered off through a pad of Celite® and the solvent was evaporated in vacuo to dryness to give Compound (4) as a white amorphous (285 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.18-1.74 (6H, m), 1.42 (3x3H, s), 2.13 (2H, m), 2.38 (2H, m), 5.01 (1H, m), 6.62 (1H, d, J=8 Hz), 7.34-7.58 (4H, m), 7.82 (1H, d, J=7.5 Hz), 8.17 (1H, br);

MASS (ES+): m/e 412.

Preparation 5

To a stirred solution of Compound (4) (242 mg) in N,N-dimethylformamide (4 mL) were added O-benzylhydroxylamine hydrochloride (141 mg), HOBT (119 mg) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (WSCD, 137 mg) and the mixture was stirred at ambient temperature for 15 hr. The reaction mixture was diluted with ethyl acetate and washed successively with water, saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogencarbonate solution and brine.

The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform:methanol = 10:1) to give Compound (5) as a pale yellow amorphous (257 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.16-1.65 (6H, m), 1.43 (3x3H, s), 1.70-2.25 (4H, m), 4.69-5.00 (3H, m), 5.52-5.75 (1H, m), 7.24-8.18 (10H, m), 8.53 (1H, br), 9.10-9.30 (1H, br);

MASS (ES+): m/e 517.

Preparation 6

To a stirred solution of Compound (5) (244 mg) in dioxane (6 mL) was added 4N-hydrogen chloride in dioxane (2 mL), and the mixture was stirred at ambient temperature for 2 hr. The solvent was evaporated in vacuo to give Compound (6) hydrochloride as a pale yellow amorphous (254 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.16-1.54 (6H, m), 1.93 (2H, t, J=7 Hz), 2.14 (2H, m), 4.72 (1H, m), 4.75 (2H, s), 7.28-7.42 (5H, m), 7.57 (1H, dd, J=8, 7 Hz), 7.69 (1H, dd, J=8, 7 Hz), 7.78-7.88 (2H, m), 8.08 (1H, d, J=8 Hz), 8.48 (1H, d, J=8 Hz), 8.94 (2H, br), 10.99 (1H, br);

MASS (ES+): m/e 417.

Preparation 7

To a stirred solution of Compound (6) (218 mg) in N,N-dimethylformamide (5 mL) were added HOBT (78 mg), WSCD (90 mg) and 4-(methoxycarbonyl)benzoic acid (95 mg), and the resulting mixture was stirred at ambient temperature for 15 hr. This mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, washed successively with water, saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogencarbonate solution and brine. The organic phase was dried over sodium sulfate, and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (2:1 to 1:1) to give Compound (7) as a pale yellow amorphous (193 mg). The obtained Compound (7) was used in Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.24-1.60 (6H, m), 1.95 (2H, t,

J=6.5 Hz), 2.06 (1H, m), 2.21 (1H, m), 3.89 (3H, s), 4.76 (2H, s), 5.40 (1H, m), 7.28-7.50 (6H, m), 7.52-7.78 (3H, m), 7.97 (1H, m), 8.03-8.15 (4H, m), 8.40 (1H, m), 9.19 (1H, d, J=8 Hz), 10.94 (1H, s), 12.61 (0.5H, s), 13.11 (0.5H, s);
MASS (ES+): m/e 579.

Preparation 8

To a stirred solution of Compound (7) (133 mg) in methanol (3 mL) was added 1N-sodium hydroxide (0.46 mL), and the mixture was stirred at ambient temperature for 7 hr. The mixture was neutralized with 1N-hydrogen chloride and extracted with ethyl acetate. The organic phase was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo to give Compound (8) (115 mg). The obtained Compound (8) was used in Example 2.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.60 (6H, m), 1.85-2.30 (4H, m), 4.77 (2H, s), 5.41 (1H, m), 7.26-7.50 (6H, m), 7.52-7.78 (3H, m), 7.92-8.14 (5H, m), 8.40 (1H, br-d, J=7 Hz), 9.17 (1H, d, J=7.5 Hz), 10.95 (1H, s), 12.64 (0.5H, s), 13.18 (0.5H, s);
MASS (ES+): m/e 563.

Preparation 9

To a stirred solution of (7S)-7-amino-N-(benzyloxy)-7-(3H-naphtho[1,2-d]imidazol-2-yl)heptanamide (111 mg) in dichloromethane (3 mL) were added triethylamine (0.045 mL) and then methanesulfonyl chloride in dichloromethane (1 ml) at 0°C. The mixture was stirred at the same temperature for 1 hr and left at ambient temperature for 15 hr. The resulting mixture was washed successively with saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogencarbonate solution and brine. The organic phase was dried over sodium sulfate. The solvent was evaporated in vacuo, and the residue was purified by preparative thin layer chromatography to give Compound (9) as a pale yellow amorphous (114 mg). The obtained Compound (9) was used in Example 3.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.16-1.58 (6H, m), 1.85-2.05 (4H, m), 2.74 (3x0.4H, s), 2.81 (3x0.6H, s), 4.65 (1H, m), 4.76 (2H, s),

7.28-7.42 (5H, m), 7.46 (1H, m), 7.54-7.84 (5H, m), 7.99 (1H, dd, J=7.5, 7.5 Hz), 8.35 (0.4H, d, J=8 Hz), 8.42 (0.6H, d, J=8 Hz), 10.93 (1H, br-s), 12.61 (0.6H, s), 13.13 (0.4H, s);
MASS (ES+): m/e 495.

Preparation 10

Compound (10) (338 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (10) was used in Example 4.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26-1.60 (6H, m), 1.96 (2H, t, J=6.5 Hz), 2.07 (1H, m), 2.22 (1H, m), 3.90 (3H, s), 4.76 (2H, s), 5.42 (1H, m), 7.28-7.50 (6H, m), 7.53-7.76 (4H, m), 7.98 (1H, d, J=7, 7 Hz), 8.13 (1H, d, J=8 Hz), 8.25 (1H, d, J=8 Hz), 8.40 (1H, m), 8.58 (1H, m), 9.24 (1H, d, J=7.5 Hz), 10.94 (1H, s), 12.61 (0.6H, s), 13.11 (0.4H, s);
MASS (ES+): m/e 579.

Preparation 11

Compound (11) (659 mg) was obtained in a manner similar to Preparation 2.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.30-1.52 (4H, m), 1.47 (3x3H, s), 1.55-1.77 (3H, m), 1.95 (1H, m), 2.37 (2H, t, J=7 Hz), 3.97 (2H, br), 4.17 (1H, dt, J=7, 7 Hz), 5.05 (1H, d, J=7 Hz), 5.11 (0.5H, s), 5.12 (0.5H, s), 6.83 (0.5H, d, J=8 Hz), 6.96-7.03 (1H, m), 7.22-7.58 (11.5H, m), 7.91 (0.5H, s), 7.96 (0.5H, s);
MASS (ES+): m/e 546.

Preparation 12

Compound (12) (591 mg) was obtained in a manner similar to Preparation 3.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.21-1.46 (4H, m), 1.40 (3x3H, s), 1.48-1.62 (2H, m), 1.70-1.84 (2H, m), 1.86-2.00 (2H, m), 2.35 (2H, t, J=7.3 Hz), 4.75 (1H, m), 5.07 (2H, s), 7.28-7.84 (14H, m), 12.22 (1H, br);
MASS (ES+): m/e 528.

Preparation 13

Compound (13) (478 mg) was obtained in a manner similar to Preparation 3.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.20-1.55 (6H, m), 1.40 (3x3H, s),

1.70-2.00 (2H, m), 2.19 (2H, t, J=7 Hz), 4.75 (1H, m), 7.27-7.38 (2H, m), 7.40-7.86 (7H, m);

MASS (ES+): m/e 438.

Preparation 14

Compound (14) (456 mg) was obtained in a manner similar to Preparation 5.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.16-1.54 (6H, m), 1.40 (3x3H, s), 1.70-2.01 (4H, m), 4.74 (1H, m), 4.77 (2H, s), 7.27-7.82 (14H, m), 10.94 (1H, s), 12.21 (0.5H, s), 12.22 (0.5H, s);

MASS (ES+): m/e 543.

Preparation 15

Compound (15) (353 mg) was obtained in a manner similar to Preparation 6.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.14-1.56 (6H, m), 1.69 (1H, m), 1.81 (1H, m), 1.93 (2H, m), 4.01 (1H, m), 4.77 (2H, s), 7.28-7.80 (13H, m), 11.95 (1H, br);

MASS (ES+): m/e 443.

Preparation 16

Compound (16) (173 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (16) was used in Example 5.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.20-1.58 (6H, m), 1.95 (3H, t, J=7.3 Hz), 2.00 (1H, m), 2.14 (1H, m), 4.77 (2H, s), 5.32 (1H, m), 7.29-7.72 (15.5H, m), 7.83 (0.5H, s), 7.97 (2H, d, J=7.7 Hz), 8.91 (1H, d, J=8 Hz), 10.95 (1H, s), 12.31 (0.5H, s), 12.34 (0.5H, s);

MASS (ES+): m/e 547.

Preparation 17

Compound (17) (53 mg) was obtained in a manner similar to Preparation 5. The obtained Compound (17) was used in Example 6.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.18-1.60 (6H, m), 1.64-2.02 (2H, m), 2.04-2.39 (2H, m), 4.86 (2H, s), 5.45 (1H, m), 7.18-7.46 (12H, m), 7.62 (1H, d, J=8.5 Hz), 7.82 (2x1H, d, J=7.5 Hz), 7.85 (1H, d, J=9 Hz), 9.23 (1H, br);

MASS (ES+): m/e 521.

Preparation 18

A solution of Compound (10) (116 mg) in 40% methylamine in methanol (6 mL) was stirred at ambient temperature for 3 hr. The solvent was evaporated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform:methanol = 10:1) to give Compound (18) as a pale yellow amorphous (126 mg). The obtained Compound (18) was used in Example 7.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26-1.58 (6H, m), 1.90-2.42 (4H, m), 2.80 (3H, d, J=4.5 Hz), 4.71-4.94 (2H, m), 5.41 (1H, m), 7.28-7.76 (10H, m), 7.90-8.13 (3H, m), 8.31-8.58 (3H, m), 9.06 (1H, m), 10.94 (1H, m), 12.61 (0.6H, s), 13.12 (0.4H, s);

MASS (ES+): m/e 578.

Preparation 19

Compound (19) (531.6 mg) was obtained in a manner similar to Preparation 2.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.32-1.51 (4H, m), 1.46 (9H, s), 1.60-1.75 (3H, m), 1.86-2.00 (1H, m), 2.37 (2H, t, J=7.3 Hz), 4.07-4.17 (1H, m), 4.25 (2H, s), 5.04-5.11 (1H, m), 5.11 (2H, s), 6.75 (1H, d, J=8.1 Hz), 7.23-7.31 (2H, m), 7.30-7.42 (5H, m), 7.48 (1H, s), 7.97 (1H, s);

MASS (ES+): m/e 538.22 (M+1).

Preparation 20

Compound (20) (663 mg) was obtained in a manner similar to Preparation 3.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.28-1.51 (4H, m), 1.45 (9H, s), 1.57-1.76 (4H, m), 1.87-2.06 (1H, m), 2.10-2.26 (1H, m), 2.34 (2H, t, J=7.4 Hz), 4.76-4.88 (1H, m), 5.10 (2H, s), 5.29 (1H, d, J=7.7 Hz), 7.28-7.40 (5H, m), 7.40-7.52 (2H, m), 7.60-7.83 (1H, m), 7.99 (0.4H, s), 10.74-10.63 (0.6H, br);

MASS (ES+): m/e 520.21 (M+1).

Preparation 21

Compound (21) (629 mg) was obtained in a manner similar to Preparation 6.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.85-1.14 (2H, m), 1.16-1.56 (4H, m),

2.24 (2H, t, J=7.0 Hz), 2.29-2.44 (2H, m), 3.71 (2H, s), 5.03 (2H, s), 5.53 (1H, br), 7.25-7.41 (5H, m), 7.71 (1H, d, J=8.4 Hz), 7.90 (1H, d, J=8.4 Hz), 8.11 (1H, s), 9.12-9.80 (1H, br);
MASS (ES+): m/e 420.10 (free).

Preparation 22

Compound (22) (473 mg) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.17-1.67 (6H, m), 1.79 (1H, brs), 2.03-2.39 (2H, m), 2.82 (2H, t, J=7.6 Hz), 5.07 (2H, s), 5.33-5.47 (1H, m), 7.25-7.55 (10H, m), 7.66-7.88 (1H, m), 7.80 (2H, d, J=8.4 Hz), 7.86 (0.5H, s), 11.58-11.85 (0.5H, m);
MASS (ES+): m/e 524.39 (M+1).

Preparation 23

To a solution of benzyl (7S)-7-(benzoylamino)-7-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]heptanoate (473 mg) in methanol (5 mL) was added 10% palladium on barium sulfate (48 mg) and the mixture was stirred under hydrogen atmosphere at ambient temperature for 2 hr. The catalyst was filtered off through a pad of Celite®. The solvent was evaporated in vacuo, and the residue was purified by preparative thin layer chromatography (hexane:ethyl acetate = 10:1) to give Compound (23) (397 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.27-1.60 (6H, m), 1.94-2.26 (2H, m), 2.19 (2H, t, J=7.3 Hz), 5.27-5.39 (1H, m), 7.44-7.61 (4H, m), 7.63-7.77 (1H, m), 7.79-7.93 (1H, m), 7.96 (1H, d, J=8.1 Hz), 8.98 (2H, d, J=8.1 Hz), 11.84-12.92 (1H, br);
MASS (ES+): m/e 434.39 (M+1).

Preparation 24

To a solution of Compound (23) (394 mg) in N,N-dimethylformamide (6 mL) were added HOBT (160 mg) and WSCD-HCl (227 mg), and the mixture was stirred for 1 hr. To the mixture was added tetrahydropyranyloxyamine (160 mg) and the mixture was stirred for 1 hr. To the mixture were added additional tetrahydropyranyloxyamine (1.5 equivalents), HOBT (1.3 equivalent) and WSCD-HCl (1.3 equivalents), and the mixture was stirred for 3 hr. The residue was purified by preparative thin

layer chromatography (chloroform:methanol=10:1) to give Compound (24) (568 mg). The obtained Compound (24) was used in Example 8.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.24-1.76 (12H, m), 1.92-2.22 (4H, m), 3.44-3.54 (1H, m), 3.84-3.96 (1H, m), 4.79 (1H, s), 5.27-5.39 (1H, m), 7.44-7.61 (5H, m), 7.61-7.83 (1H, m), 7.92-8.03 (3H, m), 8.32 (0.2H, s), 8.96 (1H, d, J=8.1 Hz), 10.90 (0.8H, s);

MASS (ES+): m/e 533.38 (M+1).

Preparation 25

Compound (25) (596.3 mg) was obtained in a manner similar to Preparation 2.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.49-1.55 (5H, m), 1.62-1.76 (3H, m), 1.84-2.01 (1H, m), 2.37 (2H, t, J=7.3 Hz), 4.05-4.20 (3H, m), 4.95-5.06 (1H, m), 5.12 (2H, s), 6.51 (1H, dd, J=9.2, 8.1 Hz), 6.84-6.93 (1H, m), 7.29-7.41 (5H, m), 7.84 (1H, s);

MASS (ES+): m/e 506.15 (M+1).

Preparation 26

Compound (26) (600 mg) was obtained in a manner similar to Preparation 3.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.34-1.46 (4H, m), 1.44 (6H, s), 1.45 (3H, s), 1.57-1.72 (2H, m), 1.88-2.06 (1H, m), 2.10-2.29 (1H, m), 2.34 (1H, t, J=7.3 Hz), 2.35 (1H, t, J=7.3 Hz), 4.70-4.84 (1H, m), 5.11 (2H, s), 5.12-5.31 (1H, m), 7.00-7.11 (2H, m), 7.31-7.42 (5H, m), 10.40-10.57 (1H, m);

MASS (ES+): m/e 488.15 (M+1).

Preparation 27

Compound (27) (521 mg) was obtained in a manner similar to Preparation 6.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.92-1.57 (6H, m), 2.12-2.40 (4H, m), 3.71 (1H, s), 5.04 (2H, s), 5.26-5.42 (1H, m), 7.21-7.38 (7H, m), 7.45-7.57 (1H, m);

MASS (ES+): m/e 388.09 (free).

Preparation 28

Compound (28) (397 mg) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.11-1.67 (6H, m), 2.08-2.37 (2H, m),

2.25 (2H, t, J=7.3 Hz), 5.06 (2H, s), 5.32-5.52 (1H, m), 6.92-7.11 (2H, m), 7.24-7.42 (7H, m), 7.47 (2H, dd, J=6.2, 7.3 Hz), 7.55-7.69 (0.4H, m), 7.77-7.94 (0.6H, m), 7.81 (1H, d, J=7.7 Hz), 8.16-8.21 (0.1H, m), 11.88-12.00 (0.7H, m), 12.04-12.27 (0.2H, m);

MASS (ES+): m/e 492.24 (M+1).

Preparation 29

Compound (29) (327 mg) was obtained in a manner similar to Preparation 23.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.26-1.58 (6H, m), 1.91-2.25 (2H, m), 2.19 (2H, t, J=7.0 Hz), 5.23-5.34 (1H, m), 7.14-7.34 (2H, m), 7.45-7.65 (3H, m), 7.96 (2H, d, J=8.4 Hz), 8.90-9.07 (1H, m), 11.92-12.27 (0.4H, m), 12.69 (0.6H, brs);

MASS (ES-): m/e 400.20 (M-1).

Preparation 30

Compound (30) (116 mg) was obtained in a manner similar to Preparation 24. The obtained Compound (30) was used in Example 9.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.73 (12H, m), 1.92-2.19 (2H, m), 1.97 (2H, t, J=6.6 Hz), 3.42-3.53 (1H, m), 3.85-3.95 (1H, m), 4.79 (1H, s), 5.22-5.32 (1H, m), 7.16-7.30 (2H, m), 7.46-7.60 (3H, m), 7.93-8.01 (2H, m), 8.92-9.00 (1H, m), 10.88-10.95 (0.6H, m), 12.65-12.72 (0.4H, m).

Preparation 31

Compound (31) (104.8 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (31) was used in Example 10.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.22-1.60 (6H, m), 1.88-2.32 (4H, m), 4.77 (2H, s), 5.34-5.47 (1H, m), 7.29-7.78 (11H, m), 7.94-8.02 (1H, m), 8.30 (1H, d, J=8.4 Hz), 8.34-8.45 (1H, m), 8.71-8.78 (1H, m), 9.13 (1H, s), 9.21 (1H, d, J=8.4 Hz), 10.95 (0.6H, s), 12.62 (0.2H, s), 13.11 (0.2H, s);

MASS (ES+): m/e 522.35 (M+1).

Preparation 32

Compound (32) (109.5 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (32) was used in Example

11.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.25-1.59 (6H, m), 1.91-2.14 (1H, m), 1.95 (2H, t, J=7.3 Hz), 2.15-2.31 (1H, m), 4.77 (2H, s), 5.30-5.43 (1H, m), 7.25-7.40 (5H, m), 7.41-7.50 (1H, m), 7.52-7.77 (3H, m), 7.85-7.91 (2H, m), 7.94-8.02 (1H, m), 8.33-8.47 (1H, m), 8.73-8.81 (2H, m), 9.31 (1H, d, J=8.1 Hz), 10.95 (0.5H, brs), 12.64 (0.3H, brs), 13.13 (0.2H, brs);

MASS (ES+): m/e 522.18 (M+1).

<u>Preparation 33</u>

Compound (33) (116 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (33) was used in Example 12.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.20-1.55 (6H, m), 1.82-2.24 (4H, m), 4.75 (2H, s), 5.38-5.50 (1H, m), 7.28-7.42 (5H, m), 7.42-7.51 (1H, m), 7.53-7.79 (4H, m), 7.94-8.15 (4H, m), 8.23-8.50 (1H, m), 8.72 (1H, dd, J=4.8, 1.1 Hz), 9.05-9.22 (1H, m), 10.93 (0.6H, brs), 12.70 (0.2H, brs), 13.19 (0.2H, brs);

MASS (ES+): m/e 522.32 (M+1).

<u>Preparation 34</u>

Compound (34) (432.1 mg) was obtained in a manner similar to Preparation 2.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.31-1.53 (4H, m), 1.46 (9H, s), 1.53-1.76 (3H, m), 1.85-2.01 (1H, m), 2.39 (1H, t, J=7.3 Hz), 4.07 (1H, dt, J=8.1, 6.2 Hz), 4.51 (2H, brs), 5.03 (1H, d, J=6.2 Hz), 5.12 (2H, s), 6.72 (1H, d, J=8.4 Hz), 7.31-7.41 (5H, m), 7.31 (1H, dd, J=8.4, 1.8 Hz), 7.52 (1H, d, J=1.8 Hz), 7.86 (1H, s);

MASS (ES+): m/e 495.19 (M+1).

<u>Preparation 35</u>

Compound (35) (467 mg) was obtained in a manner similar to Preparation 3.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.33-1.51 (4H, m), 1.45 (9H, s), 1.56-1.74 (2H, m), 1.90-2.07 (1H, m), 2.08-2.27 (1H, m), 2.35 (2H, t, J=7.3 Hz), 4.75-4.86 (1H, m), 5.11 (2H, s), 5.17-5.29 (1H, m), 7.29-7.39 (6H, m), 7.40-7.52 (2H, m), 8.04 (0.6H, s), 10.62-10.74 (0.4H, m);

MASS (ES+): m/e 477.20 (M+1).

Preparation 36

Compound (36) (474 mg) was obtained in a manner similar to Preparation 6.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.18-1.37 (4H, m), 1.44-1.58 (2H, m), 1.93-2.09 (2H, m), 2.32 (2H, t, J=7.3 Hz), 4.56-4.70 (1H, m), 5.05 (2H, s), 7.30-7.41 (5H, m), 7.65 (1H, dd, J=8.4, 1.5 Hz), 7.79 (1H, d, J=8.4 Hz), 8.21 (1H, s), 8.72-8.86 (3H, m);

MASS (ES+): m/e 377.14 (free).

Preparation 37

Compound (37) (411 mg) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.20-1.69 (6H, m), 1.72-2.39 (2H, m), 2.29 (2H, t, J=7.3 Hz), 5.07 (2H, s), 5.36-5.51 (1H, m), 7.25-7.62 (11H, m), 7.66-7.88 (1H, m), 7.80 (2H, d, J=7.7 Hz), 7.99 (0.6H, s), 11.83-12.04 (0.4H, m);

MASS (ES+): m/e 481.19 (M+1).

Preparation 38

Compound (38) (302 mg) was obtained in a manner similar to Preparation 23.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.25-1.59 (6H, m), 1.92-2.23 (2H, m), 2.19 (2H, t, J=7.3 Hz), 5.31 (1H, dt, J=8.1, 5.5 Hz), 7.43-7.60 (5H, m), 7.66 (1H, d, J=8.1 Hz), 7.96 (2H, d, J=8.4 Hz), 8.05 (1H, brs), 8.99 (1H, d, J=8.1 Hz);

MASS (ES+): m/e 391.12 (M+1).

Preparation 39

Compound (39) (339 mg) was obtained in a manner similar to Preparation 24. The obtained Compound (39) was used in Example 13.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.14-1.74 (12H, m), 1.90-2.22 (4H, m), 3.42-3.45 (1H, m), 3.82-3.96 (1H, m), 4.79 (1H, s), 5.26-5.38 (1H, m), 6.00 (1H, br), 7.46-7.79 (5H, m), 7.93-8.19 (2.5H, m), 8.95 (1H, d, J=8.1 Hz), 10.75 (0.3H, brs), 12.79 (0.2H, br);

MASS (ES+): m/e 490.21 (M+1).

Preparation 40

Compound (40) (102 mg) was obtained in a manner similar to

Preparation 7. The obtained Compound (40) was used in Example 14. ^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.23-1.60 (6H, m), 1.88-2.29 (2H, m), 1.94 (2H, t, J=7.3 Hz), 2.97 (6H, s), 4.76 (2H, s), 5.31-5.44 (1H, m), 6.72 (2H, d, J=9.2 Hz), 7.28-7.49 (6H, m), 7.52-7.78 (3H, m), 7.84 (2H, d, J=9.2 Hz), 7.92-8.01 (1H, m), 8.35-8.43 (1H, m), 8.50-8.59 (1H, m), 10.94 (0.5H, s), 12.51 (0.3H, s), 13.06 (0.2H, s);

MASS (ES+): m/e 564.32 (M+1).

Preparation 41

Compound (41) (154 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (41) was used in Example 15. ^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.60 (6H, m), 1.95 (2H, t, J=7.0 Hz), 1.97-2.31 (2H, m), 4.77 (2H, s), 5.36-5.50 (1H, m), 7.04 (1H, dd, J=7.3, 7.0 Hz), 7.20 (1H, dd, J=8.1, 7.3 Hz), 7.27-7.40 (7H, m), 7.40-7.49 (2H, m), 7.53-7.77 (5H, m), 7.93-8.03 (1H, m), 8.34-8.45 (1H, m), 8.95 (1H, d, J=7.3 Hz), 10.94 (0.7H, s), 11.61 (1H, s), 12.64 (0.2H, brs), 13.15 (0.1H, brs);

MASS (ES+): m/e 560.29 (M+1).

Preparation 42

Compound (42) (117 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (42) was used in Example 16. ^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.20-1.57 (6H, m), 1.93 (2H, d, J=7.0 Hz), 2.00-2.29 (2H, m), 4.75 (2H, s), 5.38-5.49 (1H, m), 7.26-7.40 (5H, m), 7.45 (1H, dd, J=7.7, 7.7 Hz), 7.58 (1H, dd, J=7.7, 7.7 Hz), 7.63-7.79 (2H, m), 7.98 (1H, d, J=7.7 Hz), 8.27-8.47 (1H, m), 8.80 (1H, d, J=2.6 Hz), 8.92 (1H, d, J=2.6 Hz), 9.18-9.37 (1H, m), 9.25 (1H, s), 10.93 (0.7H, brs), 12.65 (0.2H, brs), 13.12 (0.1H, brs);

MASS (ES+): m/e 523.26 (M+1).

Preparation 43

Compound (43) (139 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (43) was used in Example 17. ^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.83 (3H, t, J=6.6 Hz), 1.16-1.42 (8H, m), 1.41-1.62 (4H, m), 1.77-2.30 (6H, m), 4.77 (2H, s), 5.07-5.22 (1H, m), 7.28-7.40 (5H, m), 7.40-7.49 (1H, m), 7.52-

7.75 (2H, m), 7.65 (1H, s), 7.93-8.01 (1H, m), 8.32-8.44 (2H, m), 10.94 (0.5H, s), 12.51 (0.3H, s), 13.06 (0.2H, s);
MASS (ES+): m/e 515.22 (M+1).

Preparation 44

To a stirred solution of (7S)-amino-N-(benzyloxy)-7-(3H-naphtho[1,2-d]imidazol-2-yl)heptanamide (120 mg) in methylene chloride (2 mL) were added acetic anhydride (0.054 mL) and pyridine (0.047 mL), and the mixture was stirred at ambient temperature for 2 hr. The mixture was poured into water and extraxted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium hydrogencarbonate solution, water and brine, and dried over sodium sulfate. The solvent was evaporated in vacuo. The residue was purified by preparative thin layer chromatography ($CHCl_3$:methanol=9:1) to give Compound (44) (120 mg). The obtained Compound (44) was used in Example 18.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.20-1.55 (6H, m), 1.75-2.13 (2H, m), 1.91 (3H, s), 1.93 (2H, t, J=7.3 Hz), 4.77 (2H, s), 5.04-5.19 (1H, m), 7.30-7.40 (5H, m), 7.40-7.50 (1H, m), 7.52-7.79 (2H, m), 7.65 (1H, s), 7.93-8.02 (1H, m), 8.32-8.44 (1H, m), 8.46 (1H, d, J=8.4 Hz), 10.94 (0.5H, brs), 12.53-12.59 (0.3H, m), 13.05-13.13 (0.2H, m);
MASS (ES+): m/e 459.19 (M+1).

Preparation 45

To a stirred solution of (7S)-amino-N-(benzyloxy)-7-(3H-naphtho[1,2-d]imidazol-2-yl)heptanamide (120 mg) in chloroform (3 mL) was added a solution of phenyl isocyanate (41.2 mg) in chloroform (0.5 mL). The mixture was stirred for 2 hr. The solvent was evaporated, and the residue was triturated with diisopropyl ether and dried to give Compound (45) as a white powder (153 mg). The obtained Compound (45) was used in Example 19.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.20-1.61 (6H, m), 1.82-2.07 (2H, m), 1.93 (2H, t, J=7.3 Hz), 4.75 (2H, s), 4.98-5.14 (1H, m), 6.82 (1H, d, J=7.7 Hz), 6.89 (2H, dd, J=7.3, 7.3 Hz), 7.22 (2H, dd, J=7.3, 7.3 Hz), 7.27-7.43 (7H, m), 7.46 (1H, dd, J=8.1, 7.7 Hz), 7.59

(1H, dd, J=8.1, 7.7 Hz), 7.62-7.78 (2H, m), 7.99 (1H, d, J=8.1 Hz), 8.33-8.45 (1H, m), 8.68 (1H, s), 10.92 (1H, s);
MASS (ES+): m/e 536.25 (M+1).

Preparation 46

Compound (46) (161 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (46) was used in Example 20.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.00-2.31 (20H, m), 4.77 (2H, s), 5.06-5.20 (1H, m), 7.28-7.50 (6H, m), 7.74-7.52 (3H, m), 7.93-8.02 (2H, m), 8.25 (1H, d, J=8.0 Hz), 8.31-8.43 (1H, m);
MASS (ES+): m/e 527.33 (M+1).

Preparation 47

Compound (47) (142 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (47) was used in Example 21.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.82 (3H, t, J=6.6 Hz), 1.13-1.40 (10H, m), 1.39-1.61 (4H, m), 1.77-2.10 (4H, m), 2.08-2.30 (2H, m), 4.77 (2H, s), 5.08-5.22 (1H, m), 7.28-7.40 (5H, m), 7.40-7.50 (1H, m), 7.51-7.74 (3H, m), 7.65 (1H, s), 7.94-8.01 (1H, m), 8.32-8.43 (2H, m), 10.94 (0.5H, s), 12.51 (0.3H, s), 13.06 (0.2H, s);
MASS (ES+): m/e 529.36 (M+1).

Preparation 48

Compound (48) (96 mg) was obtained in a manner similar to Preparation 44. The obtained Compound (48) was used in Example 22.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.10-1.37 (4H, m), 1.38-1.57 (2H, m), 1.84-2.16 (4H, m), 2.86 (6H, s), 4.77 (2H, s), 4.98-5.07 (1H, m), 6.66 (1H, s, J=9.2 Hz), 7.29-7.41 (5H, m), 7.40-7.70 (3H, m), 7.76 (1H, s), 7.94-8.06 (1H, m), 8.35-8.44 (2H, m), 10.90-11.00 (1H, m);

MASS (ES+): m/e 488.26 (M+1).

Preparation 49

Compound (49) (101 mg) was obtained in a manner similar to Preparation 44. The obtained Compound (49) was used in Example 23.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.99 (3H, t, J=7.0 Hz), 1.15-1.35 (6H, m), 1.38-1.56 (2H, m), 1.72-2.04 (4H, m), 2.97-3.09 (1H, m),

4.76 (2H, s), 4.92-5.06 (1H, m), 6.00 (1H, t, J=5.5 Hz), 6.37-6.47 (1H, m), 7.26-7.41 (6H, m), 7.40-7.49 (1H, m), 7.52-7.75 (3H, m), 7.92-8.02 (1H, m), 8.29-8.44 (1H, m), 10.92 (0.6H, s), 12.56 (0.3H, s), 13.09 (0.1H, s);

MASS (ES+): m/e 488.22 (M+1).

Preparation 50

Compound (50) (160 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (50) was used in Example 24.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.23-1.59 (6H, m), 1.88-2.29 (4H, m), 2.36 (3H, s), 4.76 (2H, s), 5.31-5.46 (1H, m), 7.29 (2H, d, J=8.1 Hz), 7.32-7.39 (5H, m), 7.40-7.49 (1H, m), 7.51-7.68 (2H, m), 7.64 (1H, s), 7.72 (1H, d, J=9.2 Hz), 7.88 (2H, d, J=8.1 Hz), 7.92-8.02 (1H, m), 8.34-8.43 (1H, m), 8.82-8.90 (1H, m), 10.94 (0.5H, s), 12.55 (0.3H, s), 13.08 (0.2H, s);

MASS (ES+): m/e 535.31 (M+1).

Preparation 51

Compound (51) (62.8 mg) was obtained in a manner similar to Preparation 9. The obtained Compound (51) was used in Example 25.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.89-1.22 (4H, m), 1.21-1.40 (2H, m), 1.67-1.93 (4H, m), 4.41-4.53 (1H, m), 4.75 (2H, s), 7.24-7.49 (9H, m), 7.50-7.67 (3H, m), 7.67-7.80 (2H, m), 7.93-7.99 (1H, m), 8.23-8.43 (2H, m), 10.90 (0.6H, s), 12.47 (0.3H, s), 12.94 (0.1H, s);

MASS (ES+): m/e 557.24 (M+1).

Preparation 52

Compound (52) (62.8 mg) was obtained in a manner similar to Preparation 48. The obtained Compound (52) was used in Example 26.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.15-1.41 (6H, m), 1.18 (3H, t, J=6.6 Hz), 1.40-1.57 (2H, m), 1.77-2.11 (2H, m), 1.94 (2H, t, J=7.3 Hz), 3.93-4.10 (2H, m), 4.77 (2H, s), 4.78-4.92 (1H, m), 7.28-7.51 (6H, m), 7.51-7.79 (4H, m), 7.97 (1H, dd, J=7.7, 6.2 Hz), 8.38 (1H, dd, J=8.1, 7.7 Hz), 10.94 (0.5H, s), 12.51 (0.3H, s), 13.02 (0.2H, s);

MASS (ES+): m/e 489.20 (M+1).

Preparation 53

Compound (53) (116 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (53) was used in Example 27.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.10-1.59 (6H, m), 1.22 (6H, d, J=6.6 Hz), 1.89-2.30 (2H, m), 1.95 (2H, t, J=7.7 Hz), 2.87-3.03 (1H, m), 4.76 (2H, s), 5.32-5.46 (1H, m), 7.27-7.40 (7H, m), 7.51-7.69 (2H, m), 7.65 (1H, s), 7.73 (1H, d, J=8.8 Hz), 7.91 (2H, d, J=8.1 Hz), 7.97 (1H, dd, J=7.7, 7.0 Hz), 8.39 (1H, dd, J=7.7, 7.3 Hz), 8.81-8.90 (1H, m), 10.94 (0.5H, s), 12.53 (0.3H, s), 13.06 (0.2H, s);
MASS (ES+): m/e 563.30 (M+1).

Preparation 54

Compound (54) (116 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (54) was used in Example 28.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.21-1.61 (6H, m), 1.85-2.40 (4H, m), 2.35 (1H, s), 2.36 (2H, s), 4.77 (2H, s), 5.27-5.43 (1H, m), 7.19-7.51 (10H, m), 7.52-7.77 (2H, m), 7.67 (1H, s), 7.73 (1H, d, J=7.7 Hz), 7.92-8.04 (1H, m), 8.35-8.45 (1H, m), 8.73-8.83 (1H, m), 10.95 (0.5H, s), 12.56 (0.3H, s), 13.12 (0.2H, s);
MASS (ES+): m/e 535.35 (M+1).

Preparation 55

Compound (55) (149 mg) was obtained in a manner similar to Preparation 48. The obtained Compound (55) was used in Example 29.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.59 (6H, m), 1.95 (2H, t, J=7.3 Hz), 1.98-2.29 (2H, m), 2.37 (3H, s), 4.76 (2H, s), 5.33-5.45 (1H, m), 7.29-7.40 (4H, m), 7.41-7.49 (1H, m), 7.52-7.61 (1H, m), 7.62-7.80 (3H, m), 7.97 (1H, d, J=8.1 Hz), 8.32 (0.6H, s), 8.40 (1H, d, J=8.4 Hz), 8.89 (1H, d, J=8.1 Hz), 10.93 (0.4H, s);
MASS (ES+): m/e 535.31 (M+1).

Preparation 56

Compound (56) (252 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (56) was used in Example 30.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.20-1.41 (4H, m), 1.41-1.59 (2H, m), 1.80-2.01 (3H, m), 2.00-2.31 (1H, m), 2.09 (3H, s), 4.56 (2H, dd,

J=17.9, 2.9 Hz), 4.77 (2H, s), 5.10-5.24 (1H, m), 7.27-7.41 (6H, m), 7.41-7.51 (1H, m), 7.53-7.76 (3H, m), 7.97 (1H, d, J=7.7 Hz), 8.31-8.44 (1H, m), 8.59-8.69 (1H, m), 10.93 (0.5H, s), 12.59 (0.3H, s), 13.07 (0.2H, s);

MASS (ES+): m/e 517.21 (M+1).

Preparation 57

Compound (57) (147 mg) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.19-1.40 (4H, m), 1.40-1.57 (2H, m), 1.78-2.00 (3H, m), 1.99-2.24 (1H, m), 2.09 (3H, s), 4.56 (2H, s), 4.76 (2H, s), 5.09-5.24 (1H, m), 7.28-7.40 (6H, m), 7.40-7.50 (1H, m), 7.52-7.77 (3H, m), 7.97 (1H, d, J=7.7 Hz), 8.30-8.45 (1H, m), 8.57-8.70 (1H, m), 10.93 (0.5H, s), 12.58 (0.3H, s), 13.06 (0.2H, s);

MASS (ES+): m/e 517.22 (M+1).

Preparation 58

Compound (58) (80 mg) was obtained in a manner similar to Preparation 8. The obtained Compound (58) was used in Example 31.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.13-1.39 (4H, m), 1.39-1.56 (2H, m), 1.86-2.12 (2H, m), 1.93 (2H, t, J=7.3 Hz), 3.93 (2H, s), 4.76 (2H, s), 5.19-5.32 (1H, m), 7.27-7.43 (6H, m), 7.45-7.55 (1H, m), 7.58-7.68 (1H, m), 7.68-7.79 (2H, m), 8.02 (1H, d, J=8.4 Hz), 8.15-8.24 (1H, m), 8.41 (1H, d, J=8.4 Hz), 10.94 (1H, s);

MASS (ES+): m/e 475.27 (M+1).

Preparation 59

Compound (59) (143 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (59) was used in Example 32.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.19-1.4 (4H, m), 1.40-1.57 (2H, m), 1.82-2.13 (2H, m), 1.93 (2H, t, J=7.0 Hz), 3.40 (3H, s), 3.92 (2H, s), 4.76 (2H, s), 5.16-5.29 (1H, m), 7.27-7.41 (6H, m), 7.41-7.51 (1H, m), 7.53-7.75 (2H, m), 7.66 (1H, s), 7.93-8.02 (1H, m), 8.14-8.27 (1H, m), 8.29-8.44 (1H, m), 10.93 (0.5H, s), 12.57 (0.3H, s), 13.07 (0.2H, s);

MASS (ES+): m/e 489.20 (M+1).

Preparation 60

Compound (60) (82 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (60) was used in Example 33.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.16-1.40 (4H, m), 1.40-1.58 (2H, m), 1.81-2.10 (4H, m), 2.24 (3H, s), 2.26 (3H, s), 2.88-3.04 (2H, m), 4.76 (2H, s), 5.15-5.27 (1H, m), 7.28-7.41 (6H, m), 7.41-7.51 (1H, m), 7.53-7.77 (2H, m), 7.66 (1H, s), 7.94-8.03 (1H, m), 8.11-8.23 (1H, m), 8.27-8.43 (1H, m), 10.93 (0.5H, s), 12.60 (0.3H, s), 13.10 (0.2H, s);
MASS (ES+): m/e 502.27 (M+1).

Preparation 61

Compound (61) (75 mg) was obtained in a manner similar to Preparation 48. The obtained Compound (61) was used in Example 34.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.89 (6H, d, J=6.6 Hz), 1.18-1.41 (4H, m), 1.41-1.57 (2H, m), 1.68-2.09 (5H, m), 3.66-3.85 (2H, m), 4.68-4.92 (1H, m), 4.77 (2H, s), 7.28-7.51 (7H, m), 7.52-7.79 (3H, m), 7.65 (1H, s), 7.92-8.02 (1H, m), 8.33-8.44 (1H, m), 10.94 (0.5H, s), 12.52 (0.3H, s), 13.04 (0.2H, s);
MASS (ES+): m/e 517.29 (M+1).

Preparation 62

Compound (62) (131.4 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (62) was used in Example 35.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.01 (3H, d, J=6.3 Hz), 1.06 (3H, d, J=6.6 Hz), 1.18-1.39 (4H, m), 1.40-1.56 (2H, m), 1.78-2.12 (5H, m), 4.76 (2H, s), 5.07-5.22 (1H, m), 7.28-7.40 (6H, m), 7.40-7.50 (1H, m), 7.52-7.76 (3H, m), 7.65 (1H, s), 7.94-8.01 (1H, m), 8.28-8.43 (2H, m), 10.93 (0.5H, s), 12.51 (0.3H, s), 13.08 (0.2H, s);
MASS (ES+): m/e 487.30 (M+1).

Preparation 63

Compound (63) (124.7 mg) was obtained in a manner similar to Preparation 48. The obtained Compound (63) was used in Example 36.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.16 (9H, s), 1.21-1.39 (4H, m), 1.40-1.57 (2H, m), 1.86-2.14 (4H, m), 4.77 (2H, s), 5.13-5.28 (1H, m), 7.29-7.49 (6H, m), 7.51-7.77 (3H, m), 7.79-7.89 (1H, m), 7.93-8.02 (1H, m), 8.30-8.45 (1H, m), 10.94 (0.5H, s), 12.50 (0.3H, s), 13.14 (0.2H, s);

MASS (ES+): m/e 501.27 (M+1).

Preparation 64

Compound (64) (124.7 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (64) was used in Example 37.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.11-1.35 (4H, m), 1.35-1.56 (2H, m), 1.71-2.10 (2H, m), 1.93 (2H, t, J=7.3 Hz), 2.37-2.59 (2H, m), 2.76-2.93 (2H, m), 4.77 (2H, s), 5.07-5.22 (1H, m), 7.08-7.27 (5H, m), 7.28-7.50 (6H, m), 7.52-7.76 (3H, m), 7.93-8.02 (1H, m), 8.30-8.48 (2H, m), 10.94 (0.5H, s), 12.53 (0.3H, s), 13.07 (0.2H, s);

MASS (ES+): m/e 549.34 (M+1).

Preparation 65

Compound (65) (311 mg) was obtained in a manner similar to Preparation 48. The obtained Compound (65) was used in Example 38.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.16 (3H, t, J=7.0 Hz), 1.21-1.56 (6H, m), 1.79-2.14 (2H, m), 1.94 (2H, t, J=7.3 Hz), 3.29 (1H, d, J=15.4 Hz), 3.39 (1H, d, J=15.4 Hz), 4.07 (2H, q, J=7.0 Hz), 4.76 (2H, s), 5.07-5.21 (1H, m), 7.28-7.41 (5H, m), 7.41-7.51 (1H, m), 7.53-7.78 (3H, m), 7.94-8.02 (1H, m), 8.41 (1H, d, J=8.1 Hz), 8.72 (1H, d, J=8.1 Hz), 10.93 (0.5H, s), 12.60 (0.3H, s), 13.10 (0.2H, s);

MASS (ES+): m/e 531.33 (M+1).

Preparation 66

Compound (66) (115 mg) was obtained in a manner similar to

Preparation 7. The obtained Compound (66) was used in Example 39. ^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.13-1.35 (4H, m), 1.36-1.53 (2H, m), 1.74-2.11 (4H, m), 2.83 (6H, s), 4.76 (2H, s), 5.04-5.21 (1H, m), 6.64 (2H, d, J=8.1 Hz), 7.09 (1H, d, J=8.1 Hz), 7.12 (1H, d, J=8.1 Hz), 7.28-7.40 (6H, m), 7.40-7.51 (1H, m), 7.53-7.77 (3H, m), 7.94-8.02 (1H, m), 8.30-8.45 (1H, m), 8.51-8.59 (1H, m), 10.92 (0.5H, s), 12.57 (0.3H, s), 13.09 (0.2H, s);
MASS (ES+): m/e 578.39 (M+1).

Preparation 67

Compound (67) (141 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (67) was used in Example 40.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.21-1.57 (6H, m), 1.88-2.29 (2H, m), 1.95 (2H, t, J=7.0 Hz), 4.76 (2H, s), 5.28-5.40 (1H, m), 6.96 (1H, s), 7.31-7.51 (6H, m), 7.52-7.82 (4H, m), 7.94-8.03 (1H, m), 8.29 (1H, s), 8.34-8.45 (1H, m), 8.70 (1H, d, J=8.1 Hz), 10.94 (0.5H, s), 12.60 (0.3H, s), 13.12 (0.2H, s);
MASS (ES+): m/e 511.17 (M+1).

Preparation 68

Compound (68) (146.9 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (68) was used in Example 41.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.24-1.44 (4H, m), 1.43-1.57 (2H, m), 1.87-2.31 (4H, m), 4.76 (2H, s), 5.27-5.41 (1H, m), 6.65 (1H, dd, J=3.7, 1.5 Hz), 7.24 (1H, d, J=3.7 Hz), 7.28-7.41 (6H, m), 7.40-7.51 (1H, m), 7.53-7.78 (3H, m), 7.88 (1H, d, J=1.5 Hz), 7.94-8.02 (1H, m), 8.32-8.49 (1H, m), 8.76-8.88 (1H, m), 10.94 (0.7H, s), 12.58 (0.2H, s), 13.09 (0.1H, s);
MASS (ES+): m/e 511.19 (M+1).

Preparation 69

Compound (69) (136.8 mg) was obtained in a manner similar to Preparation 8. The obtained Compound (69) was used in Example 42.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.12-1.56 (6H, m), 1.78-2.12 (2H, m), 1.93 (2H, t, J=6.6 Hz), 3.22 (1H, d, J=15.0 Hz), 3.31 (1H, d, J=15.0 Hz), 4.76 (2H, s), 5.08-5.19 (1H, m), 7.29-7.41 (5H, m),

7.45 (1H, dd, J=7.7, 8.1 Hz), 7.58 (1H, dd, J=7.7, 8.1 Hz), 7.62-7.76 (2H, m), 7.98 (1H, d, J=7.7 Hz), 8.34-8.42 (1H, m), 8.69 (1H, d, J=7.7 Hz), 10.92 (1H, s);
MASS (ES+): m/e 503.23 (M+1).

Preparation 70

Compound (70) (87.2 mg) was obtained in a manner similar to Preparation 9. The obtained Compound (70) was used in Example 43.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.98-1.11 (3H, m), 1.14-1.54 (6H, m), 1.84-2.02 (4H, m), 2.69-2.94 (2H, m), 4.54-4.69 (1H, m), 4.76 (2H, s), 7.26-7.39 (5H, m), 7.42-7.51 (1H, m), 7.53-7.85 (4H, m), 7.93-8.03 (1H, m), 8.30-8.46 (1H, m), 10.94 (0.5H, s), 12.62 (0.3H, s), 13.15 (0.2H, s);
MASS (ES+): m/e 509.23 (M+1).

Preparation 71

Compound (71) (91.1 mg) was obtained in a manner similar to Preparation 9. The obtained Compound (71) was used in Example 44.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.69 (3H, t, J=7.3 Hz), 1.17-1.61 (8H, m), 1.84-2.03 (2H, m), 1.93 (2H, t, J=7.3 Hz), 2.59-2.97 (2H, m), 4.55-4.66 (1H, m), 4.76 (2H, s), 7.29-7.42 (6H, m), 7.41-7.51 (1H, m), 7.53-7.77 (3H, m), 7.80 (1H, d, J=8.4 Hz), 7.98 (1H, dd, J=7.7, 7.3 Hz), 8.30-8.46 (1H, m), 10.93 (0.5H, s), 12.62 (0.3H, s), 13.14 (0.2H, s);
MASS (ES+): m/e 523.24 (M+1).

Preparation 72

To a solution of (7S)-7-amino-N-(benzyloxy)-7-(3H-naphtho[1,2-d]imidazol-2-yl)heptanamide (120 mg) in dichloromethane (2 mL) were added succinic anhydride, molecular sieves (4A, powder) and triethylamine (87.5 mg), and the mixture was refluxed for 15 hr. To the reaction mixture was added 10% aqueous citric acid solution and extracted with chloroform. The organic layer was washed with saturated aqueous sodium hydrogencarbonate solution, water and brine and concentrated in vacuo to give Compound (72) as a gummy substance. The obtained Compound (72) was used in Example 45.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.18-1.40 (4H, m), 1.39-1.55 (2H, m),

1.76-2.12 (4H, m), 2.32-2.56 (4H, m), 4.76 (2H, s), 5.05-5.19 (1H, m), 7.32-7.51 (7H, m), 7.53-7.83 (3H, m), 7.94-8.02 (1H, m), 8.31-8.51 (1H, m), 8.45 (1H, d, J=7.7 Hz), 10.93 (0.8H, s), 12.02-12.22 (1H, br), 12.48 (0.1H, s), 1.98 (0.1H, s);

MASS (ES+): m/e 517.26 (M+1).

Preparation 73

Compound (73) (148.7 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (73) was used in Example 46.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.23-1.58 (6H, m), 1.86-2.34 (4H, m), 4.76 (2H, s), 5.29-5.43 (1H, m), 6.81 (2H, d, J=8.8 Hz), 7.26-7.41 (6H, m), 7.39-7.49 (1H, m), 7.51-7.77 (3H, m), 7.84 (2H, d, J=8.8 Hz), 7.92-8.01 (1H, m), 8.34-8.44 (1H, m), 8.61-8.70 (1H, m), 10.01 (1H, s), 10.94 (0.5H, s), 12.51 (0.3H, s), 13.05 (0.2H, s);

MASS (ES+): m/e 537.25 (M+1).

Preparation 74

Compound (74) (116 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (74) was used in Example 47.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.14-1.37 (4H, m), 1.32 (6H, s), 1.37-1.52 (2H, m), 1.80-2.05 (2H, m), 1.91 (2H, t, J=6.6 Hz), 4.75 (2H, s), 5.10-5.21 (1H, m), 7.27-7.39 (5H, m), 7.41-7.51 (1H, m), 7.54-7.76 (3H, m), 7.94-8.09 (2H, m), 8.23-8.44 (1H, m), 10.93 (0.5H, s), 12.62 (0.3H, s), 13.15 (0.2H, s);

MASS (ES+): m/e 503.23 (M+1).

Preparation 75

Compound (75) (138 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (75) was used in Example 48.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.19-1.59 (6H, m), 1.95 (2H, t, J=7.3 Hz), 1.97-2.12 (1H, m), 2.13-2.30 (1H, m), 4.76 (2H, s), 5.32-5.47 (1H, m), 7.29-7.41 (6H, m), 7.40-7.49 (1H, m), 7.52-7.77 (3H, m), 7.99 (1H, d, J=8.1 Hz), 7.99 (1H, d, J=8.4 Hz), 8.12 (2H, d, J=8.4 Hz), 8.33-8.44 (1H, m), 9.26 (1H, d, J=8.4 Hz), 10.94 (0.5H, s), 12.63 (0.3H, s), 13.12 (0.2H, s);

MASS (ES+): m/e 546.22 (M+1).

Preparation 76

Compound (76) (28 mg) was obtained in a manner similar to Preparation 7. The obtained Compound (76) was used in Example 49. ^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.11-1.43 (4H, m), 1.42-1.61 (2H, m), 1.81-2.07 (2H, m), 2.09-2.47 (2H, m), 2.74 (3H, brs), 2.89 (1H, brs), 4.79 (2H, s), 5.33-5.46 (1H, m), 7.29-7.52 (7H, m), 7.52-7.82 (3H, m), 7.90-8.07 (1H, m), 8.29-8.49 (1H, m), 10.96 (0.5H, s), 12.60 (0.3H, s), 12.85 (0.2H, s);
MASS (ES+): m/e 499.18 (M+1).

Preparation 77

To a solution of benzyl (1S)-5-(tert-butyldimethylsilyl)oxy-1-(5-phenyl-1H-benzimidazol-2-yl)-pentylcarbamate (3.0 g) in N,N-dimethylformamide (50 mL) was added potassium t-butoxide (805 mg) under ice-cooling, and the mixture was stirred at 0°C for 30 min. To the mixture were added 3,4-dimethoxybenzyl bromide (1.91 g) and tetrabutylammonium iodide (TBAI, 408 mg), and the mixture was stirred at 0°C for 3 hr. The reaction was quenched by adding saturated aqueous ammonium chloride solution, and the reaction mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over sodium sulfate. The dried mixture was filtered, and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (eluting with $CHCl_3$:ethyl acetate=95:5 then 9:1). The resulting solid was triturated with diethyl ether to give Compound (77) (1.64 g). ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.01 (6H, s), 0.85 (9H, s), 1.19-1.54 (4H, m), 1.88-2.06 (2H, m), 3.50 (2H, t, J=5.9 Hz), 3.77 (3H, s), 3.83 (3H, s), 5.00 (1H, d, J=12.1 Hz), 5.04-5.18 (1H, m), 5.10 (1H, d, J=12.1 Hz), 5.40-5.59 (1H, m), 5.50 (1H, d, J=16.5 Hz), 5.53 (1H, d, J=16.5 Hz), 6.63 (1H, dd, J=8.4, 1.3 Hz), 6.73 (1H, d, J=1.4 Hz), 6.75 (1H, d, J=8.4 Hz), 7.23-7.38 (6H, m), 7.39-7.64 (5H, m), 7.53 (1H, d, J=8.4 Hz), 7.80 (1H, d, J=8.4 Hz);
MASS (ES+): m/e 694.46 (M+1).

Preparation 78

A suspension of benzyl (1S)-5-{[tert-

butyldimethylsilyl]oxy}-1-[1-(3,4-dimethoxybenzyl)-5-phenyl-1H-benzimidazol-2-yl]pentylcarbonate (2.73 g) and 10% palladium on carbon (270 mg) in methanol (50 mL) and acetic acid (12 mL) was stirred under hydrogen atmosphere at ambient temperature for 30 min. The catalyst was removed through a pad of Celite®, and the solvent was evaporated. The residue was diluted with ethyl acetate, washed with saturated aqueous sodium hydrogencarbonate solution (x3), water and brine, and dried over sodium sulfate. The mixture was filtered and the solvent was evaporated to give Compound (78) (1.89 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.01 (6H, s), 0.85 (9H, s), 1.21-1.58 (4H, m), 1.76-2.06 (2H, m), 3.55 (2H, t, J=5.9 Hz), 3.78 (2H, s), 3.78 (1H, s), 3.83 (2H, s), 3.84 (1H, s), 4.06-4.17 (1H, m), 5.35-5.51 (2H, m), 6.52-6.62 (1H, m), 6.66-6.72 (1H, m), 6.72-6.80 (1H, m), 7.23-7.37 (1H, m), 7.38-7.68 (5H, m), 7.51 (1H, d, J=8.4 Hz), 7.82 (1H, d, J=8.4 Hz);

MASS (ES+): m/e 560.24 (M+1).

Preparation 79

Compound (79) (1.97 mg) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.03 (6H, s), 0.82 (9H, s), 1.29-1.57 (4H, m), 2.03-2.23 (2H, m), 3.51-3.58 (2H, m), 3.63 (3H, s), 3.67 (2H, s), 3.69 (1H, s), 5.51-5.65 (1H, m), 5.56 (1H, d, J=16.1 Hz), 5.66 (1H, d, J=16.1 Hz), 6.65-6.71 (1H, m), 6.80-6.88 (1H, m), 6.89-6.97 (1H, m), 7.32-7.58 (7H, m), 7.65-7.76 (3H, m), 7.76-7.94 (3H, m), 9.04-9.12 (1H, m);

MASS (ES+): m/e 664.41 (M+1).

Preparation 80

To a solution of Compound (79) (1.97 g) in tetrahydrofuran (20 mL) was added tetrabutylammonium fluoride (TBAF, 5.34 g) and the mixture was stirred for 2 hr. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over sodium sulfate and filtered. The solvent was evaporated to give a crude compound. The compound was crystallized from hexane to give

Compound (80) (1.48 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.25-1.69 (6H, m), 2.06-2.21 (2H, m), 3.65 (3H, s), 3.68 (2H, s), 3.70 (1H, s), 4.40 (1H, t, J=5.1 Hz), 5.52-5.71 (1H, m), 5.58 (1H, d, J=16.1 Hz), 5.62 (1H, d, J=16.1 Hz), 6.68-6.75 (1H, m), 6.82-6.88 (1H, m), 6.90-6.96 (1H, m), 7.32-7.40 (1H, m), 7.42-7.59 (6H, m), 7.66-7.79 (4H, m), 7.84-7.94 (2H, m), 9.05-9.13 (1H, m);

MASS (ES+): m/e 550.21 (M+1).

Preparation 81

Compound (80) was dissolved in a mixture of methylene chloride (10 ml) and dimethyl sulfoxide (4 ml) with heating in a water bath. To the solution were added periodinane (702 mg) and sodium hydrogencarbonate (139 mg) and the mixture was stirred at ambient temperature for 3 hr. The reaction was quenched by adding a 20% solution of sodium thiosulfate in saturated aqueous sodium hydrogencarbonate solution under ice-cooling. The mixture was stirred for 15 min under ice-cooling and extracted with ethyl acetate. The aqueous layer was separated, and the organic layer was washed with a 20% solution of sodium thiosulfate in saturated aqueous sodium hydrogencarbonate solution, saturated aqueous sodium hydrogencarbonate solution, water and brine, and dried over sodium sulfate. The mixture was filtered and the solvent was evaporated to give Compound (81) (700 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 9.62 (1H, s), 9.06 (1H, d, J=8.1 Hz), 7.78-7.91 (2H, m), 7.62-7.77 (4H, m), 7.39-7.54 (6H, m), 7.29-7.36 (1H, m), 6.85-6.91 (1H, m), 6.77-6.82 (1H, m), 6.62-6.68 (1H, m), 5.62 (1H, d, J=16.1 Hz), 5.52 (1H, d, J=16.1 Hz), 5.48-5.62 (1H, m), 3.66 (1H, s), 3.64 (2H, s), 3.59 (2H, s), 3.59 (1H, s), 2.39-2.50 (2H, m), 2.04-2.19 (2H, m), 1.51-1.71 (2H, m);

MASS (ES+): m/e 548.16 (M+1).

Preparation 82

To a solution of Compound (82) (700 mg) in tetrahydrofuran (30 mL) was added methyl(triphenylphosphoranylidene)acetate, and the mixture was stirred for 6 hr and left standing for a week. The solvent was evaporated, and the residue was purified by a

silica gel column ($CHCl_3$:methanol=95:5 then 9:1) and triturated with diisopropyl ether to give Compound (82) (783 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.42-1.59 (2H, m), 2.05-2.30 (4H, m), 3.60 (3H, s), 3.63 (4H, s), 3.66 (2H, s), 5.47 (1H, d, J=16.5 Hz), 5.47-5.63 (1H, m), 5.63 (1H, d, J=16.5 Hz), 5.80-5.90 (1H, m), 6.61-6.68 (1H, m), 6.77-6.94 (3H, m), 7.29-7.78 (11H, m), 7.80-7.91 (2H, m), 9.05-9.14 (1H, m);

MASS (ES+): m/e 604.27 (M+1).

Preparation 83

Compound (83) (232 mg) was obtained in a manner similar to Preparation 8.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.34-1.56 (2H, m), 2.05-2.23 (4H, m), 3.61 (3H, s), 3.64 (2H, s), 3.66 (1H, s), 5.46-5.65 (2H, m), 5.71-5.78 (1H, m), 6.64-6.68 (1H, m), 6.78-6.94 (3H, m), 7.40-7.94 (13H, m), 9.04-9.14 (1H, m);

MASS (ES+): m/e 590.17 (M+1).

Preparation 84

A solution of Compound (83) (227 mg) in a mixed solvent (acetonitrile (2.8 mL), methanol (0.6 mL) and water (0.6 mL)) was added cerium ammonium nitrate (CAN, 633 mg) and the mixture was stirred at ambient temperature overnight. To the mixture was added additional CAN (3 equivalent) and stirred at ambient temperature for 3 hr. The solvent was evaporated, and the residue was dissolved in methanol. To the solution was added 1N aqueous sodium hydroxide solution under ice-cooling and the mixture was stirred for 2 days. The mixture was neutralized with 1N aqueous hydrogen chloride solution and extracted with ethyl acetate. The extract was washed with water and brine, and purified by thin layer chromatography ($CHCl_3$:methanol=9:1) to give Compound (84) (65.4 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.33-1.67 (2H, m), 1.94-2.45 (4H, m), 5.28-5.40 (1H, m), 5.79 (1H, d, J=15.8 Hz), 6.83 (1H, dt, J=15.8, 7.0 Hz), 7.29-7.38 (1H, m), 7.40-7.89 (8H, m), 7.67 (2H, d, J=7.3 Hz), 7.97 (2H, d, J=7.3 Hz), 8.91-9.00 (1H, m), 12.07-12.45 (1H, m);

MASS (ES+): m/e 440.14 (M+1).

Preparation 85

Compound (85) (64.3 mg) was obtained in a manner similar to Preparation 8.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.33-1.68 (2H, m), 1.94-2.45 (4H, m), 5.27-5.40 (1H, m), 5.79 (1H, d, J=15.8 Hz), 6.84 (1H, dt, J=15.8, 7.0 Hz), 7.29-7.37 (1H, m), 7.41-7.87 (8H, m), 7.67 (2H, d, J=7.7 Hz), 7.97 (2H, d, J=7.0 Hz), 8.90-9.00 (1H, m), 12.12-12.42 (1H, m);

MASS (ES+): m/e 440.12 (M+1).

Preparation 86

Compound (86) (82 mg) was obtained in a manner similar to Preparation 24. The obtained Compound (86) was used in Example 50.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.21-1.74 (8H, m), 1.88-2.32 (4H, m), 3.44-3.58 (1H, m), 3.84-3.97 (1H, m), 4.77-4.86 (1H, m), 5.28-5.40 (1H, m), 5.76-5.85 (1H, m), 6.65-6.77 (1H, m), 7.29-7.37 (1H, m), 7.41-7.79 (10H, m), 7.97 (2H, d, J=8.1 Hz), 8.89-9.00 (1H, m), 10.95-11.07 (0.4H, m), 12.29-12.41 (0.6H, m);

MASS (ES+): m/e 539.22 (M+1).

Preparation 87

Benzyl (7S)-7-(5-benzoyl-1H-benzimidazol-2-yl)-7-[(tert-butoxycarbonyl)amino]heptanoate (1.6 g) was added 10% hydrogen chloride in methanol (48 mL) under ice-cooling, and the mixture was stirred at ambient temperature 24 hr. The solvent was evaporated. The residue was dissolved in methanol and the solvent was evaporated (these steps were repeated several times) to remove excess hydrogen chloride. The residue was dried in a vacuum dryer to give Compound (87) (1.64 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.19-1.36 (4H, m), 1.40-1.57 (2H, m), 1.95-2.11 (2H, m), 2.27 (2H, t, J=7.3 Hz), 3.56 (3H, s), 4.57-4.69 (1H, m), 7.55-7.63 (2H, m), 7.66-7.80 (5H, m), 7.99 (1H, s), 8.82 (2H, br);

MASS (ES+): m/e 380.11 (free).

Preparation 88

Compound (88) (403 mg) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.28-1.48 (4H, m), 1.47-1.61 (2H, m), 1.94-2.08 (1H, m), 2.08-2.23 (1H, m), 2.29 (2H, t, J=7.3 Hz), 3.56 (3H, s), 5.32 (1H, dt, J=8.8, 5.9 Hz), 7.46-7.78 (11H, m), 7.83 (0.4H, s), 7.90-8.01 (2H, m), 8.92-9.00 (1H, m), 12.59 (0.3H, s), 12.69 (0.3H, s);

MASS (ES+): m/e 484.17 (M+1).

Preparation 89

A solution of methyl (7S)-7-(benzoylamino)-7-(5-benzoyl-1H-benzimidazol-2-yl)heptanoate (398 mg) in a mixed solvent (methanol (3.6 mL) and acetic acid (0.4 mL)) was hydrogenated for 20 hr. The mixture was filtered through a pad of Celite® and the filtrate was reduced again with a catalytic amount of palladium on carbon at room temperature at 3 atm for 2 days. The solvent was evaporated, and the residue was extracted with ethyl acetate and water. The organic phase was washed with a saturated aqueous sodium hydrogencarbonate solution, water and brine, and dried over sodium sulfate. The mixture was filtered, and the solvent was evaporated to give Compound (89) (277 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26-1.45 (4H, m), 1.45-1.59 (2H, m), 1.88-2.02 (1H, m), 2.02-2.17 (1H, m), 2.28 (2H, t, J=7.3 Hz), 3.55 (3H, s), 5.25 (1H, dt, J=8.4, 6.2 Hz), 5.77 (0.5H, d, J=4.0 Hz), 5.78 (0.5H, d, J=4.0 Hz), 5.81 (0.5H, d, J=4.0 Hz), 5.84 (0.5H, d, J=4.0 Hz), 7.08-7.22 (2H, m), 7.23-7.33 (2H, m), 7.33-7.40 (2H, m), 7.41-7.59 (5H, m), 7.94 (2H, d, J=8.1 Hz), 8.84 (1H, d, J=8.4 Hz), 12.15 (1H, s);

MASS (ES+): m/e 487.17 (M+1).

Preparation 90

Compound (90) (207 mg) was obtained in a manner similar to Preparation 8.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.43 (4H, m), 1.43-1.57 (2H, m), 1.89-2.03 (1H, m), 2.03-2.14 (1H, m), 2.18 (2H, t, J=7.3 Hz), 5.78 (1H, d, J=4.0 Hz), 5.84 (1H, d, J=4.0 Hz), 7.10-7.22 (2H, m),

7.23-7.33 (2H, m), 7.34-7.44 (2H, m), 7.43-7.59 (5H, m), 7.94 (2H, d, J=7.0 Hz), 8.85 (1H, d, J=8.1 Hz), 11.98 (1H, s), 12.26 (1H, br);

MASS (ES+): m/e 472.15 (M+1).

Preparation 91

Compound (91) (190 mg) was obtained in a manner similar to Preparation 24. The obtained Compound (91) was used in Example 51.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.21-1.71 (12H, m), 1.87-2.17 (2H, m), 1.96 (2H, t, J=7.3 Hz), 3.42-3.52 (1H, m), 3.84-3.95 (1H, m), 4.79 (1H, s), 5.25 (1H, dt, J=8.1, 6.2 Hz), 5.75-5.87 (2H, m), 7.08-7.22 (2H, m), 7.23-7.33 (2H, m), 7.33-7.40 (2H, m), 7.40-7.59 (5H, m), 7.94 (2H, d, J=7.0 Hz), 8.85 (1H, d, J=8.1 Hz), 10.90 (0.5H, s), 12.16 (0.5H, s);

MASS (ES+): m/e 571.23 (M+1).

Preparation 92

To a solution of dimethyl methylphosphonate (58.5 g) in tetrahydrofuran (708 mL) was added dropwise a solution of n-buthyllithium (1.59 M hexane solution, 326 mL) over 1 hr at -78°C. After stirring for 30 min, ethyl fluoroacetate (50 g) was added dropwise over 1 hr at -78°C. After stirring for 30 min, the reaction mixture was warmed to room temperature, and water (78.5 mL) was added thereto and the mixture was and stirred for 20 min. The reaction mixture was acidified with concentrated hydrochloric acid to pH 3 and was extracted with dicholoromethane ten times. The combined organic layer was dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by distillation under reduced pressure (90-93°C/ 0.3 mmHg) to give Compound (92) as a colorless oil (54 g). The obtained compound (92) was used in Preparation 100.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.25 (2H, dd, J=22.7, 3.7 Hz), 3.80 (3H, s), 3.84 (3H, s), 4.84 (1H, d, J=1 Hz), 5.00 (1H, d, J=1 Hz).

Preparation 93

To a solution of 1,2-benzenediamine (34.7 g) in methylene chloride (500 mL) was added dropwise a solution of 1-

(((benzyloxy)carbonyl)oxy)-2,5-pyrrolidinedione (40 g) in methylene chloride (150 mL) over 1 hr with cooling in an ice bath. The reaction mixture was stirred at ambient temperature for 2 hr. The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with aqueous 0.1N-hydrochloric acid, saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated in vacuo. The solid formed was washed with diethyl ether to give Compound (93) as a white solid (30 g). The obtained compound (93) was used in Preperation 102.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 3.50-3.90 (1H, brs), 5.20 (2H, s), 6.30-6.50 (1H, brs), 6.77-6.83 (2H, m), 7.03 (1H, ddd, J=7.3, 1.5, 1.5 Hz), 7.28-7.45 (7H, m).

Preparation 94

To a solution of 6-hydroxy-L-norleucine (50.17 g), benzyl chloroformate (37.8 g) in dioxane-water (500 mL - 500 mL) was added sodium bicarbonate (74.5 g) with cooling in an ice bath. The reaction mixture was stirred at ambient temperature for 2 hr, and benzyl chloroformate (37.8 g) and sodium bicarbonate (37.2 g) were added to the reaction mixture with cooling in an ice bath. The reaction mixture was stirred at ambient temperature for 12 hr. The residue was partitioned between ethyl ether and water. Excess benzyl chloroformate was removed by extraction (100 mL, twice). The aqueous layer was acidified with concentrated hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N-hydrochloric acid and brine, dried over sodium sulfate, and concentrated in vacuo to give Compound (94) as a colorless oil (95 g). The obtained crude product was used in Preparation 95 without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.37-1.66 (4H, m), 1.68-1.96 (2H, m), 3.24 (1H, brs), 3.64 (2H, t, J=6.22 Hz), 4.36-4.44 (1H, m), 5.08 (1H, d, J=11.0 Hz), 5.12 (1H, d, J=11.0 Hz), 5.48 (1H, brd, J=7.7 Hz), 7.30-7.39 (5H, m).

Preparation 95

To a solution of Compound (94) (127 g) and cesium carbonate

(73.5 g) in N,N-dimethyl formamide (1000 mL) was added dropwise (bromomethyl)benzene (78.8 g) with cooling in an ice bath. The reaction mixture was stirred at ambient temperature for 12 hr. The mixture was concentrated in vacuo, and the residue was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo to give Compound (95) as a colorless oil (125 g). Water was azeotropically removed with toluene twice, and the crude residue was used in Preparation 96 without further purificatiuon.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.20-1.95 (6H, m), 3.58 (2H, t, J=5.9 Hz), 5.08-5.24 (4H, m), 5.33 (1H, brd, J=8.4 Hz), 7.28-7.4 (10H, brs);

MASS (ES+): m/e 372.2 (M+1).

Preparation 96

To a solution of Compound (95) (83 g) and pyridinium p-toluenesulfonate (1.12 g) in methylene chloride (600 mL) was added dropwise a solution of 1-ethoxyethylene (17.7 g) with cooling in an ice bath. The reaction mixture was stirred at ambient temperarute for 1 hr. The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with a mixture of chloroform and ethyl acetate (9:1) to give Compound (96) as a colorless oil (83 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.19 (3H, t, J=7.0 Hz), 1.28 (3H, d, J=5.5 Hz), 1.34-1.93 (6H, m), 3.32-3.64 (4H, m), 4.43 (1H, dd, J=7.3, 12.0 Hz), 4.64 (1H, q, J=5.5 Hz), 5.11 (2H, s), 5.15 (1H, d, J=12.5 Hz), 5.20 (1H, d, J=12.5 Hz), 5.31 (1H, brd, J=7.7 Hz), 7.25-7.40 (10H, m);

MASS (ES+): m/e 466.4 (M+Na).

Preparation 97

To a solution of Compound (96) (83 g) and 4-(N,N-

dimethylamino)pyridine (2.29 g) in acetonitrile (600 mL) was added dropwise a solution of di(tert-butyl) dicarbonate (65.4 g) over 30 min with cooling in an ice bath. The reaction mixture was stirred at ambient temperature for 12 hr. The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with a mixture of hexane and ethyl acetate (9:1) to give Compound (97) as an oil (84.3 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.19 (3H, t, J=7.0 Hz), 1.28 (3H, d, J=5.1 Hz), 1.32-1.46 (2H, m), 1.39 (9H, s), 1.50-1.64 (2H, m), 1.86-2.00 (1H, m), 2.08-2.23 (1H, m), 3.30-3.70 (4H, m), 4.64 (1H, q, J=5.3 Hz), 4.97 (1H, dd, J=9.9, 5.1 Hz), 5.07 (1H, d, J=12.5 Hz), 5.12 (1H, d, J=12.5 Hz), 5.14 (1H, d, J=12.1 Hz), 5.20 (1H, d, J=12.1 Hz), 7.24-7.38 (10H, m);

MASS (ES+): m/e 566.4 (M+Na).

<u>Preparation 98</u>

To a solution of Compound (97) (41 g) in ethanol (300 mL) was added pyridinium p-toluenesulfonate (2.84 g) with cooling in an ice bath. The reaction mixture was stirred at ambient temperature for 10 hr. The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with a mixture of hexane and ethyl acetate (7:3) to give Compound (98) as a pale yellow oil (35.8 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.35-1.45 (3H, m), 1.39 (9H, s), 1.48-1.61 (3H, m), 1.85-2.02 (1H, m), 2.06-2.22 (1H, m), 3.58 (2H, dd, J=12.1, 6.2 Hz), 4.97 (1H, dd, J=9.5, 5.1 Hz), 5.08 (1H, d, J=12.5 Hz) , 5.12 (1H, d, J=12.5 Hz), 5.14 (1H, d, J=12.5 Hz), 5.20 (1H, d, J=12.5 Hz), 7.24-7.38 (10H, m);

MASS (ES+): m/e not detected.

Preparation 99

To a solution of Compound (98) (26 g) in methylene chloride (110 mL) was added 2,2,5,5-tetramethyl pyrolidine N-oxide (862 mg) at 0°C, and then iodobenzene diacetate (19.5 g) and acetic acid (1.37 mL) were added to the mixture. The reaction mixture was stirred at ambient temperature for 12 hr. The mixture was concentrated in vacuo, diluted with ethyl acetate, poured into 20% sodium thiosulfate in saturated aqueous sodium bicarbonate solution. The product was extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. The solvent was removed under reduced pressure to give Compound (99) as a pale yellow oil (25.9 g). The product was dried by azotropic removal of water with toluene (twice). The crude product was dried by pump (1 hr), which was used in Preparation 100 without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.39 (9H, s), 1.58-1.72 (2H, m), 1.86-2.03 (1H, m), 2.08-2.22 (1H, m), 2.32-2.53 (2H, m), 4.97 (1H, dd, J=9.5, 5.1 Hz), 5.07 (1H, d, J=12.1 Hz), 5.12 (1H, d, J=12.1 Hz), 5.15 (1H, d, J=12.1 Hz), 5.20 (1H, d, J=12.1 Hz), 7.24-7.39 (10H, m), 9.70 (1H, t, J=1.54 Hz);

MASS (ES+): m/e not detected.

Preparation 100

To a solution of Compound (92) (20.3 g) and cesium carbonate (34.1 g) in isopropyl alcohol (260 mL) was added dropwise a solution of Compound (99) (25.9 g) in tetrahydrofuran (5 mL) with cooling in an ice bath. The reaction mixture was stirred at 0°C for 90 min. The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and sodium phosphate buffer solution (pH=6.86). The organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with a mixture of hexane and ethyl acetate (9:1) to give Compound (100) as a colorless oil (21.7 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.39 (9H, s), 1.43-1.63 (2H, m), 1.82-2.00 (1H, m), 2.40-2.70 (3H, m), 4.92 (2H, d, J=47.3 Hz), 4.97

(1H, dd, J=9.5, 5.5 Hz), 5.07 (1H, d, J=12.1 Hz), 5.12 (1H, d, J=12.1 Hz), 5.15 (1H, d, J=12.1 Hz), 5.20 (1H, d, J=12.1 Hz), 6.31 (1H, dddd, J=15.8,2.9, 1.5, 1.5 Hz), 6.95 (1H, ddd, J=15.8, 6.6 Hz), 7.24-7.38 (10H, m);

MASS (ES+): m/e not detected.

Preparation 101

A solution of Compound (100) (21.7 g) and 10% palladium-carbon powder (4.34 g) in dioxane (170 mL) was stirred for 1 hr under hydrogen atomosphere (3 atm). The mixture was filtered through a pad of Celite® and the filtrate was concentrated in vacuo to give Compound (101) as a colorless oil (12.6 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.28-1.52 (5H, m), 1.45 (9H, s), 1.56-1.75 (3H, m), 1.80-1.94 (1H, m), 2.55 (2H, ddd, J=7.3, 7.3, 2.6 Hz), 4.22-4.36 (1H, m), 4.80 (2H, d, J=47.6 Hz), 5.02 (1H, brd, J=8.0 Hz);

MASS (ES+): m/e 306.3 (M+1).

Preparation 102

To a solution of Compound (101) (6.0 g), Compound (93) (5.0 g) and HOBT (2.92 g) in methylene chloride (60 mL) was added WSCD hydrochloride (4.14 g) with cooling in an ice bath. The reaction mixture was stirred at ambient temperature for 12 hr. The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with 0.1N-hydrochloric acid, saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was triturated with diethyl ether to give Compound (102) as a white needle crystal (6.95 g). The obtained compound (102) was used in Preparations 103 and 109.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.28-1.46 (4H, m), 1.43 (9H, s), 1.52-1.70 (3H, m), 1.86-1.98 (1H, m), 2.52 (2H, ddd, J=7.3, 7.3, 2.6 Hz), 4.09-4.20 (1H, m), 4.76 (2H, d, J=47.6 Hz), 4.90-5.02 (1H, m), 5.21 (2H, s), 7.10-7.46 (9H, m), 7.58-7. (1H, brs), 8.30-8.40 (1H, brs);

MASS (ES+): m/e 552.6 (M+Na);

m.p. 117-118°C.

Preparation 103

(1) To a solution of Compound (102) (6.95 g) in dioxane (35 mL) was added 4N hydrogen chloride dioxane solution (60 mL) at 0 °C, and the mixture was stirred at ambient temperature for 1 hr. Solvent was removed under reduced pressure and dried by pump for 2 hr to give a hydrochloride salt as a white powder.

(2) To a suspension of the hydrochloride salt (6.95 g) in methylene chloride (70 mL) were added benzoic acid (1.85 g), HOBT (2.48 g) and WSCD (2.85 g) with cooling in an ice bath. The reaction mixture was stirred at ambient temperature for 90 min. The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with 1N hydrochloric acid, saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated in vacuo to form a solid. The solid was collected with diethyl ether to give Compound (103) (4.1 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.56 (6H, m), 1.75-1.95 (2H, m), 2.40 (2H, ddd, J=7.3, 1.5, 1.5 Hz), 4.48-4.58 (1H, m), 5.02 (2H, d, J=46.9 Hz), 5.03 (2H, s), 7.08-7.24 (2H, m), 7.30-7.60 (13H, m), 7.93 (2H, d, J=7.0 Hz), 8.71 (1H, d, J=7.0 Hz), 8.81 (1H, brs);

MASS (ES+): m/e 534.6 (M+1).

Preparation 104

To a suspension of Compound (103) (8.0 g) in acetic acid (30 mL) was added 33% hydrogen bromide acetic acid solution (30.0 mL) at 0°C with cooling in a cooling bath, and the cooling bath was removed immediately. The reaction mixture was stirred for 40 min, water (100 mL) and diethyl ether (100 mL) was added and inpurity was removed by extraction (100 mL, twice). The combined organic layer was extracted with water (2 mL, 10 times) and the combined aqueous layer was poured into saturated aqueous sodium bicarbonate solution (500 mL) - ethyl acetate (200 mL). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated in vacuo.

The resulting solid was collected with diethyl ether to give Compound (104) (4.5 g). The obtained compound (104) was used in Example 53.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.28-1.58 (6H, m), 1.76-1.88 (2H, m), 2.42 (2H, t, J=7.3 Hz), 4.48-5.48 (1H, m), 4.89 (2H, brs), 5.04 (2H, d, J=46.9 Hz), 6.53 (1H, dd, J=7.7, 7.7 Hz), 6.71 (1H, d, J=7.7 Hz), 6.92 (1H, dd, J=7.7, 7.7 Hz), 7.10 (1H, d, J=7.7 Hz), 7.42-7.60 (3H, m), 7.90-7.98 (2H, d, J=7.0 Hz), 8.58 (1H, brd, J=7.0 Hz), 9.34 (1H, brs);

MASS (ES+): m/e 400.4 (M+1).

Preparation 105

To a solution of indole (1.11 g) in dichloromethane (20 mL) were added tin(IV) chloride (1 M solution in dichloromethane) and ethyl 6-(chloroformyl)hexanoate (2.16 g), and the mixture was stirred at ambient temperature for 1 hr. The resulting mixture was diluted with chloroform, washed successively with hydrochloric acid, and diluted sodium bicarbonate and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of chloroform and ethyl acetate (4:1) to give Compound (105) (996 mg) as a solid.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.16 (3H, t, J=7Hz), 1.34 (2H, m) , 1.50-1.70 (4H, m), 2.28 (2H, t, J=7Hz), 2.83 (2H, t, J=7Hz), 4.03 (2H, q, J=7Hz), 7.10-7.23 (2H, m), 7.45 (1H, m), 8.17 (1H, m), 8.32 (1H, s);

MASS: m/z 286 (M-1).

Preparation 106

To a solution of Compound (105) (200 mg) in ethanol (5 mL) and water (1 mL) were added hydroxylamine hydrochloride (121 mg) and sodium acetate (149 mg), and the mixture was stirred at reflux temperature for 1 hr. The resulting mixture was evaporated in vacuo, diluted with ethyl acetate and washed successively with water and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of hexane and ethyl acetate

(2:1) to give Compound (106) (160 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.15 (3H, t, J=7Hz), 1.37 (2H, m), 1.48-1.60 (4H, m), 2.29 (2H, t, J=7Hz), 2.68 (2H, t, J=7Hz), 4.02 (2H, q, J=7Hz), 7.03 (1H, m), 7.12 (1H, m), 7.37 (1H, d, J=8Hz), 7.65 (1H, d, J=3Hz), 8.12 (1H, d, J=8Hz);

MASS: m/z 303 (M+1).

Preparation 107

To a solution of Compound (106) (248 mg) in ethanol (5 mL) were added 10% hydrogen chloride in methanol and 10% palladium-charcol (60 mg), and the mixture was stirred under hydrogen atomosphere (4 atm) for 1 hr. The resulting mixture was filtered through Celite® and washed with ethanol. The filtrate and washings were evaporated in vacuo to give Compound (107). The obtained compound was immediately used in Example 54 without further purification.

Preparation 108

To a stirred solution of Compound E55 (63 mg, described later in Example 55) in N,N-dimethylformamide (2 mL) was added O-benzylhydroxylamine hydrochloride (36 mg), HOAT (38 mg) and WSCD (43 mg), and the resulting mixture was stirred at ambient temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, and washed successively with 10% sodium dihydrogenphosphate solution, saturated sodium hydrogen carbonate solution, and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform : methanol = 19 : 1) to give Compound (108) (60 mg). The obtained compound (108) was used in Example 56.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.57 (6H, m), 1.90-2.05 (4H, m), 4.76 (2H, s), 5.38 (1H, q, J=7Hz), 6.94 (1H, t, J=8Hz), 7.05 (1H, t, J=8Hz), 7.27-7.52 (9H, m), 7.63 (1H, d, J=8Hz), 7.85 (1H, dd, J=2, 8Hz), 8.03 (1H, d, J=8Hz).

Preparation 109

Compound (102) (300 mg) was dissolved in 1,4-dioxane (3 mL), and 4N-HCl in 1,4-dioxane (3 mL) was added thereto at 20°C. After

stirring at 20°C for 3 hr, the solvent was removed by evaporation, and the residue was dissolved in methylene chloride (3 mL). The solution was cooled to 0°C, and diisopropylethylamine (220 mg) and mesyl chloride (78 mg) were added thereto. After stirring at 20°C for 3 hr, the mixture was partitioned between EtOAc and water. The organic layer was separated, washed with water and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel eluting with a mixture of EtOAc and hexane (1:5) to give Compound (109) (223 mg) as an oil.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.30-1.90 (8H, m), 2.49 (2H, t, J=7 Hz), 2.97 (3H, s), 4.05-4.15 (1H, m), 5.11 (2H, d, J= 47 Hz), 5.24 (2H, s), 7.20-7.35 (2H, m), 7.40-7.55 (4H, m), 7.55-7.60 2H, m), 7.70 (1H, d, J= 10 Hz), 8.92 (1H, brs), 9.73 (1H, brs).

Preparation 110

Compound (109) (200 mg) was dissolved in AcOH (1 mL), and 30% HBr in AcOH (2 mL) was added thereto at 0°C. After stirring at 20°C for 3 hr, the mixture was partitioned between EtOAc and aq $NaHCO_3$. The organic layer was separated, washed with water and brine, dried over sodium sulfate, and evaporated to give Compound (110) (143 mg) as an oil. The obtained compound (110) was used in Example 57.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.30-1.90 (8H, m), 2.51 (2H, t, J=7 Hz), 3.00 (3H, s), 4.05-4.15 (1H, m), 5.12 (2H, d, J= 47 Hz), 6.66 (1H, t, J=8 Hz), 6.82 (1H, d, J=8 Hz), 7.03 (1H, t, J=8 Hz), 7.21 (1H, d, J=8 Hz), 7.60 (1H, d, J=8 Hz), 9.43 (1H, s).

Preparation 111

To a stirred suspension of dimethyl (3R)-3-((tert-butyl(diphenyl)silyl)oxy)-2-oxobutylphosphonate (4.91 g), lithium chloride (479m g) and N,N-diisopropylethylamine (1.64 mL) in dry acetonitrile (70 mL) was added a solution of benzyl (2S)-2-(bis(tert-butoxycarbonyl)amino)-6-oxohexanoate (4.1 g) in dry acetonitrile (24 mL) at room temperature. The reaction mixture was stirred at room temperature for 38 hr under nitrogen atmosphere. The mixture was partitioned

between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash column chromatography over silica gel using n-hexane-ethyl acetate (4:1) as an eluant to give Compound (111) (3.98 g) as a colorless oil.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.02 (9H, s), 1.17 (3H, d, J=7.0 Hz), 1.32-1.47 (2H, m), 1.37 (18H, s), 1.75-1.89 (1H, m), 1.93-2.07 (1H, m), 2.17-2.30 (2H, m), 4.27 (1H, q, J=7.0 Hz), 4.88 (1H, dd, J=10.0, 5.5 Hz), 5.11 (2H, s), 6.46 (1H, d, J=16.0 Hz), 6.77 (1H, dt, J=16.0, 7.0 Hz), 7.31-7.70 (15H, m);

MASS: 766(M+Na)$^+$.

Preparation 112

Compound (111) (700 mg) was dissolved in acetonitrile (7 mL), and then magnesium chloride (17.9 mg) was added to the solution at room temperature. The reaction mixture was stirred at 50°C for 2.5 hr, and poured into 5% potassium hydrogensulfate. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo to give Compound (112) (593.1 mg) as a colorless oil.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.02 (9H, s), 1.17 (3H, d, J=7.0 Hz), 1.22-1.45 (2H, m), 1.37 (9H, s), 1.52-1.69 (2H, m), 2.09-2.19 (2H, m), 3.95-4.03 (1H, m), 4.28 (1H, q, J=7.0 Hz), 5.07 (1H, d, J=13.0 Hz), 5.14 (1H, d, J=13.0 Hz), 6.44 (1H, d, J=16.0 Hz), 6.76 (1H, dt, J=16.0, 7.0 Hz), 7.28-7.48 (12H, m), 7.52-7.62 (4H, m);

MASS: 644(M+1)$^+$.

Preparation 113

A solution of Compound (112) (580 mg) in methanol (6 mL) was hydrogenated over 10% palladium carbon (58 mg) at ambient temperature under atmospheric pressure for 6 hr. The reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo to give Compound (113) (551.6 mg) as a colorless oil.

^{1}H-NMR(300 MHz, DMSO-d_6, δ): 1.02-1.41 (6H, m), 1.04 (9H, s), 1.16

(3H, d, J=6.5 Hz),1.37 (9H, s), 1.45-1.63 (2H, m), 2.37-2.46 (2H, m), 3.77-3.87 (1H, m), 4.18 (1H, q, J=6.5 Hz), 7.01 (1H, d, J=7.5 Hz), 7.38-7.52 (6H, m), 7.54-7.62 (4H, m);
MASS: 556$(M+1)^+$.

Preparation 114

A mixture of Compound (113) (600 mg), 1,2-phenylenediamine (117 mg), HOBT (160 mg) and WSCD hydrochloride (217 mg) in N,N-dimethylformamide (12 mL) was stirred at ambient temperature for 14 hr. The reaction mixture was poured into saturated sodium hydrogen carbonate solution, and extracted with chloroform. The organic layer was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography over a silica gel with n-hexane / ethyl acetate (1:1) as an eluant to give Compound (114) (443.1 mg) as a colorless amorphous.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.00-1.69 (8H, m), 1.04 (9H, s), 1.16 (3H, d, J=6.5 Hz), 1.39 (9H, s), 2.40-2.47 (2H, m), 3.96-4.07 (1H, m), 4.18 (1H, q, J=6.5 Hz), 4.84 (2H, s), 6.53 (1H, t, J=7.0 Hz), 6.69 (1H, d, J=7.0 Hz), 6.91 (1H, t, J=7.0 Hz), 7.03 (1H, d, J=7.0 Hz), 7.07 (1H, d, J=7.0 Hz), 7.37-7.48 (6H, m), 7.53-7.62 (4H, m), 9.17 (1H, s);
MASS: 644$(M-1)^+$.

Preparation 115

Compound (114) (420 mg), xylene (4.2 mL) and acetic acid (0.42 mL) were combined. The mixture was refluxed for 4 hr with azeotropic removal of water and allowed to cool. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with a n-hexane / ethyl acetate (1:1) as eluant to give Compound (115) (351.9 mg) as a pale yellow oil. The obtained compound (115) was used in Preparations 116 and 117.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.02 (9H, s), 1.12-1.46 (6H, m), 1.14 (3H, d, J=7.0 Hz), 1.39 (9H, s), 1.65-1.81 (1H, m), 1.82-1.96 (1H, m), 2.41 (2H, t, J=7.0 Hz), 4.17 (1H, q, J=7.0 Hz),

4.65-4.77 (1H, m), 7.08-7.16 (2H, m), 7.27 (1H, d, J=7.5 Hz), 7.34-7.61 (12H, m), 12.25 (1H, s);
MASS: 626$(M-1)^+$.

Preparation 116

Compound (115) (160 mg) was dissolved in dichloromethane (1 mL), and then 4N-solution of hydrochloric acid in 1,4-dioxane (1 mL) was added to the solution under nitrogen atmosphere. The mixture was stirred at ambient temperature for 1.5 hr. The solvent was concentrated in vacuo. A mixture of the residual solid, benzoic acid (31.1 mg), HOBT (37.9 mg) and WSCD (41.5 mg) in dichloromethane (1 mL) was stirred at ambient temperature for 66 hr. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution, and extracted with chloroform. The organic layer was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative silica gel column chromatography with a chloroform / methanol (40:1) as eluant to give Compound (116) (70.9 mg) as a colorless amorphous. The obtained compound (116) was used in Example 58.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.00 (9H, s), 1.14 (3H, d, J=7.0 Hz),1.15-1.41 (6H, m), 1.88-2.02 (1H, m), 2.03-2.17 (1H, m), 2.41 (2H, t, J=7.0 Hz), 4.16 (1H, q, J=7.0 Hz), 5.23-5.34 (1H, m), 7.11-7.16 (2H, m), 7.36-7.61 (15H, m), 7.97 (2H, d, J=7.5 Hz), 8.87 (1H, d, J=7.5 Hz), 12.34 (1H, s);
MASS: 632$(M+1)^+$.

Preparation 117

Compound (117) (107.5 mg) was obtained from Compound (115) (140 mg) in manner similar to Preparation 116. The obtained compound (117) was used in Example 59.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.99 (9H, s), 1.13 (3H, d, J=7.0 Hz), 1.15-1.42 (6H, m), 1.87-2.02 (1H, m), 2.06-2.20 (1H, m), 2.41 (2H, t, J=7.0 Hz), 4.15 (1H, q, J=7.0 Hz), 5.26-5.37 (1H, m), 7.04 (1H, t, J=7.5 Hz), 7.08-7.17 (2H, m), 7.20 (1H, d, J=7.5 Hz), 7.31 (1H, s), 7.34-7.50 (8H, m), 7.51-7.60 (5H, m), 7.62 (1H, d, J=7.5 Hz), 8.86 (1H, d, J=7.5 Hz), 11.61 (1H, s), 12.30 (1H, s);

MASS: 671$(M+1)^+$.

Preparation 118

To a solution of (2S)-2-{[(benzyloxy)carbonyl]amino}-6-hydroxyhexanoic acid (5.85 g) in N,N-dimethylformamide (60 mL) were added isobutyl chloroformate (2.84 g), 4-methylmorpholine N-oxide (2.66 g) and 3,5-dichloro-1,2-benzenediamine (3.68 g), and the mixture was stirred for 30 min under ice-cooling. The resulting mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was triturated with diisopropyl ether to give Compound (118) (6.93 g) as a solid.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.20-1.79 (6H, m), 3.28-3.43 (2H, m), 4.09-4.19 (1H, m), 4.39 (1H, t, J=5.4 Hz), 4.99-5.33 (2H, m), 5.27 (1H, s), 7.23-7.26 (1H, m), 7.27-7.50 (6H, m), 7.65 (1H, d, J=7.3 Hz), 9.48 (1H, s);
MS (ES+) m/e 440.06 (M+1).

Preparation 119

A mixture of Compound (118) (7.12 g) and 1N hydrochloric acid in ethanol (120 mL) was refluxed for 4 hr. The reaction mixture was concentrated in vacuo, and the concentrate was poured into a mixture of ethyl acetate and saturated aqueous sodium hydrogen carbonate. The organic layer was separated, washed with water and brine, dried over sodium sulfate, and evaporated. The residue was triturated with diisopropyl ether to give Compound (119) (6.03 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.35-2.27 (6H, m), 2.64 (1H, brs), 3.66 (1H, brs), 4.83-5.18 (3H, m), 5.80-6.10 (1H, m), 7.11-7.44 (7H, m), 7.56 (1x0.5H, s), 11.05 (1x0.2H, s), 11.21 (1x0.3H, s);
MS (ES+) m/e 422.07 (M+1).

Preparation 120

To a solution of Compound (119) (6.03 g) in N,N-dimethylformamide (100 mL) were added tert-butyldimethylsilyl chloride (2.26 g) and imidazole (1.07 g), and the mixture was stirred at ambient temperature for 3 hr. The resulting mixture

was diluted with ethyl acetate, washed successively with water and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of chloroform and methanol (4:1) to give ethyl Compound (120) (6.93 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.01 (6H, s), 0.85 (9H, s), 1.32-1.66 (4H, m), 1.93-2.31 (2H, m), 3.52-3.63 (2H, m), 4.76-4.95 (1H, m), 5.03-5.19 (2H, m), 5.45-5.71 (1H, m), 7.18-7.40 (7H, m), 7.59 (1x0.5H, d, J=1.5 Hz), 10.36 (1x0.2H, s), 10.55 (1x0.3H, s);
MS (ES+) m/e 536.21 (M+1).

Preparation 121

To a solution of Compound (120) (6.93 g) in N,N-dimethylformamide (60 mL) was added potassium tert-butoxide (1.88 g) under ice-cooling, and the mixture was stirred for 30 min. To the mixture were added 3,4-dimethoxybenzyl bromide (4.48 g) and n-tetrabutylammonium iodide (954 mg) under ice-cooling, and the mixture was stirred for 3 hr. The resulting mixture was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by silica gel chromatography (chloroform : ethyl acetate = 9 : 1) to give Compound (121) (3.99 g).

The obtained Compound (121) was used in Preparation 123.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.01 (6H, s), 0.84 (9H, s), 1.16-1.52 (4H, m), 1.79-2.05 (2H, m), 3.50 (2H, t, J=6.2 Hz), 3.78 (3H, s), 3.85 (3H, s), 4.96-5.13 (1H, m), 5.01 (1H, d, J=12.5 Hz), 5.10 (1H, d, J=12.5 Hz), 5.34 (1H, d, J=16.5 Hz), 5.46 (1H, d, J=16.5 Hz), 5.62 (1H, d, J=9.2 Hz), 6.58 (1H, d, J=8.1 Hz), 6.67 (1H, s), 6.78 (1H, d, J=8.1 Hz), 7.19 (1H, s), 7.25-7.39 (6H, m);
MS (ES+) m/e 686.35 (M+1).

Preparation 122

A solution of benzyl {(1S)-5-{[tert-butyl(dimethyl)silyl]oxy}-1-[3-(3,4-dimethoxybenzyl)-3H-naphtho[1,2-d]imidazol-2-yl]pentyl}carbamate (10.0 g) in a mixture of methanol and acetic acid (4 :1 v/v, 200mL) was

hydrogenated over 10% palladium carbon (1.0 g) at ambient temperature under hydrogen atomosphere (3 atm) for 3 hr. The reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution, water, and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo to give Compound (122) (8.25 g) as a pale yellow oil. The obtained Compound (122) was used in Preparation 124.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.01 (6H, s), 0.84 (9H, s), 1.29-2.07 (6H, m), 3.47-3.58 (2H, m), 3.74 (3H, s), 3.83 (3H, s), 4.23 (1H, t, J=6.6 Hz), 5.51 (1H, s), 6.50-6.57 (1H, m), 6.63-6.66 (1H, m), 6.69-6.79 (1H, m), 7.38 (1H, d, J=8.8 Hz), 7.48 (1H, dd, J=8.1,7.0 Hz), 7.57-7.67 (1H, m), 7.63 (1H, d, J=8.8 Hz), 7.91 (1H, d, J=8.1 Hz), 8.65 (1H, d, J=8.8 Hz);

MS (ES+) m/e 534.33 (M+1).

Preparation 123

Compound (123) (233 mg) was obtained from Compound (121) in a manner similar to Preparation 122. The obtained Compound (123) was used in Preparation 125.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.01 (6H, s), 0.85 (9H, s), 1.22-1.57 (6H, m), 1.74-2.02 (2H, m), 3.48-3.58 (2H, m), 3.79 (1H, s), 3.85 (1H, s), 4.10-4.20 (1H, m), 5.35-5.45 (1H, m), 6.48-6.56 (1H, m), 6.60-6.67 (1H, m), 6.73-6.80 (1H, m), 7.13 (1H, s, J=1.8 Hz), 7.28 (1H, d, J=1.8 Hz);

MS (ES+) m/e 552.21 (M+1).

Preparation 124

To a stirred solution of Compound (122) (8.0 g) in N,N-dimethylformamide (100 mL) were added benzoic acid (1.92 g), HOBT (2.43 g) and WSCD hydrochloride (3.45 g), and the resulting mixture was stirred at ambient temperature for 3 hr. The reaction mixture was diluted with ethyl acetate, washed successively with 10% hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel

chromatography (chloroform : ethyl acetate = 9 : 1) to give Compound (124) (7.6 g). The obtained Compound (124) was used in Preparation 126.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.01 (3H, s), 0.03 (3H, s), 0.83 (9H, s), 1.33-1.60 (4H, m), 2.10-2.23 (2H, m), 3.53 (2H, t, J=6.6 Hz), 3.75 (3H, s), 3.82 (3H, s), 5.54 (1H, d, J=16.5 Hz), 5.65-5.78 (1H, m), 5.69 (1H, d, J=16.5 Hz), 6.60-6.68 (1H, m), 6.69-6.80 (2H, m), 7.39-7.57 (5H, m), 7.61-7.74 (2H, m), 7.76-7.84 (2H, m), 7.95 (1H, d, J=8.1 Hz), 8.65 (1H, d, J=7.0 Hz);
MS (ES+) m/e 638.31 (M+1).

Preparation 125

Compound (125) (1.62g) was obtained from Compound (123) in a manner similar to Preparation 124. The obtained Compound (125) was used in Preparation 127.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.010 (3H, s), 0.024 (3H, s), 0.83 (9H, s), 1.22-1.56 (4H, m), 1.95-2.21 (2H, m), 3.52 (2H, t, J=5.9 Hz), 3.80 (3H, s), 3.85 (3H, s), 5.40 (1H, d, J=16.1 Hz), 5.55-5.68 (1H, m), 5.60 (1H, d, J=16.1 Hz), 6.57-6.63 (1H, m), 6.70-6.79 (2H, m), 7.00 (1H, d, J=9.1 Hz), 7.25 (1H, d, J=1.8 Hz), 7.32 (1H, d, J=1.8 Hz), 7.38-7.56 (3H, m), 7.70-7.78 (2H, m);
MS (ES+) m/e 656.47 (M+1).

Preparation 126

To a stirred solution of Compound (124) (7.6 g) in tetrahydrofuran (80 mL) was added tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 24 mL) under ice-cooling, and the mixture was stirred at ambient temperature for 3 hr. Additional tetrabutylammonium fluoride (8 mL) was added thereto, and the mixture was stirred for 1 hr. The reaction mixture was diluted with water (400 mL) and extracted with chloroform (750 mL). The organic layer was washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo to give Compound (126) (6.08 g). The obtained Compound (126) was used in Preparation 128.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.25-1.53 (4H, m), 2.05-2.30 (2H, m), 3.27-3.42 (2H, m), 3.57 (3H, s), 3.65 (3H, s), 4.38 (1H, t, J=5.5

Hz), 5.53-5.71 (3H, m), 6.60-6.69 (1H, m), 6.76-6.88 (2H, m), 7.37-7.53 (4H, m), 7.57-7.76 (3H, m), 7.80-7.88 (2H, m), 7.97 (1H, d, J=8.1 Hz), 8.46 (1H, d, J=7.0 Hz), 9.11 (1H, d, J=8.4 Hz);
MS (ES+) m/e 524.31 (M+1).

Preparation 127

Compound (127) (1.39 g) was obtained from Compound (125) in a manner similar to Preparation 126. The obtained Compound (127) was used in Preparation 129.

^{1}H-NMR (300 MHz,$CDCl_3$,δ): 1.17-2.03 (6H,m), 2.03-2.16 (1H,m), 3.48-3.60 (2H,m), 3.77 (3H,s), 3.83 (3H,s), 5.38 (1H,d,J=16.5 Hz), 5.52-5.68 (1H,m), 5.59 (1H,d,J=16.5 Hz), 6.55-6.63 (1H,m), 6.68-6.79 (2H,m), 7.18 (1H,d,J=8.8 Hz), 7.25 (1H,d,J=1.5 Hz), 7.30 (1H,d,J=1.5 Hz), 7.36-7.45 (2H,m), 7.45-7.54 (1H,m), 7.70-7.81 (2H,m);
MS (ES+) m/e 542.15 (M+1).

Preparation 128

To a stirred solution of Compound (126) (6.08 g) in methylene chloride (80 mL) were added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane) (6.4 g) and sodium hydrogen carbonate (1.27 g) under ice-cooling. The mixture was stirred at ambient temperature for 2 hr. The reaction was quenched with a solution of 20% sodium thiosulfate in saturated sodium hydrogen carbonate (100 mL) under ice-cooling, then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate, water and brine, dried over sodium sulfate, and concentrated in vacuo to give Compound (128) (580 mg) as an amorphous solid. The obtained Compound (128) was used in Preparations 130, 131, 132 and 133.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.07-2.27 (2H, m), 2.28-2.51 (2H, m), 3.74 (3H, s), 3.81 (3H, s), 5.54 (1H, d, J=15.8 Hz), 5.60-5.77 (1H, m), 5.67 (1H, d, J=15.8 Hz), 6.56-6.64 (1H, m), 6.64-6.78 (2H, m), 7.18-7.30 (1H, m), 7.36-7.56 (5H, m), 7.59-7.82 (4H, m), 7.95 (1H, d, J=7.7 Hz), 8.63 (1H, d, J=8.1 Hz), 9.66 (1H, s);
MS (ES+) m/e 522.24 (M+1).

Preparation 129

Compound (129) (609 mg) was obtained from Compound (127) in a manner similar to Preparation 128. The obtained Compound (129) was used in Preparation 134.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.28-1.69 (4H, m), 1.96-2.19 (2H, m), 3.79 (3H, s), 3.75-3.84 (2H, m), 3.83 (3H, s), 5.38 (1H, d, J=16.5 Hz), 5.54-5.66 (1H, m), 5.59 (1H, d, J=16.5 Hz), 6.52-6.62 (1H, m), 6.70-6.77 (2H, m), 7.16 (1H, d, J=8.8 Hz), 7.25 (1H, d, J=1.8 Hz), 7.30 (1H, d, J=1.8 Hz), 7.37-7.46 (2H, m), 7.47-7.54 (1H, m), 7.73-7.80 (2H, m), 9.65 (1H, s);
MS (ES+) m/e 540.10 (M+1).

Preparation 130

To a stirred solution of dimethyl ((3R)-3-{[tert-butyl(diphenyl)silyl]oxy}-2-oxopentyl)phosphonate (516 mg) in a mixed solvent of tetrahydrofuran and water (40:1 v/v, 7.5 mL) was added barium hydroxide octahydrate (242 mg) in an ice bath, and the resulting mixture was stirred at ambient temperature for 45 min. To this mixture was added Compound (128) (500 mg) in the same solvent (3 mL) in an ice bath, and the mixture was stirred at ambient temperature for 2 hr. To the mixture was added 10% aqueous citric acid (50 mL), and the mixture was extracted with ethyl acetate (30 mL). The organic phase was washed with saturated sodium hydrogen carbonate solution (50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluted with ethyl acetate-hexane 1:2 v/v) to give Compound (130) as a colorless foam (430 mg). The obtained Compound (130) was used in Preparation 135.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.77 (3H, t, J=7.3 Hz), 1.02 (3x3H, s), 1.36-1.66 (4H, m), 1.99-2.26 (4H, m), 3.72 (3H, s), 3.78 (3H, s), 4.11 (1H, t, J=5.8 Hz), 5.51 (1H, d, J=16.8 Hz), 5.63 (1H, d, J=16.8 Hz), 5.70 (1H, m), 6.47 (1H, d, J=15.8 Hz), 6.55 (1H, dd, J=8, 1.8 Hz), 6.64-6.78 (3H, m), 7.15-7.81 (20H, m), 7.93 (1H, d, J=7.7 Hz), 8.62 (1H, d, J=8.3 Hz);
MS (ES+) m/e 844.

Preparation 131

Compound (131) (614 mg) was obtained from Compound (128) in a manner similar to Preparation 130. The obtained Compound (131) was used in Preparation 136.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.01 (9H, s), 1.19 (3H, d, J=6.5 Hz), 1.40-1.54 (2H, m), 2.04-2.28 (4H, m), 3.72 (3H, s), 3.78 (3H, s), 4.23 (1H, q, J=6.5 Hz), 5.51 (1H, d, J=16.5 Hz), 5.64 (1H, d, J=16.5 Hz), 5.71 (1H, m), 6.46-6.60 (2H, m), 6.64-6.85 (3H, m), 7.16 (1H, d, J=9 Hz), 7.22-7.80 (20H, m), 7.93 (1H, d, J=9 Hz).

Preparation 132

Compound (132) (458 mg) was obtained from Compound (128) in a manner similar to Preparation 130. The obtained Compound (132) was used in Preparation 137.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.04 (9H, s), 1.38-1.52 (2H, m), 1.98-2.28 (4H, m), 3.71 (3H, s), 3.76 (3H, s), 4.28 (2H, s), 5.50 (1H, d, J=17 Hz), 5.63 (1H, d, J=17 Hz), 5.70 (1H, m), 6.32 (1H, d, J=16 Hz), 6.56 (1H, dd, J=8, 1.5 Hz), 6.62-6.86 (3H, m), 7.16-7.80 (20H, m), 7.93 (1H, d, J=8 Hz), 8.61 (1H, d, J=8.5 Hz).

Preparation 133

Compound (133) (393 mg) was obtained from Compound (128) in a manner similar to Preparation 130. The obtained Compound (133) was used in Preparation 138.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.06 (3H, t, J=7.3 Hz), 1.37-1.53 (2H, m), 2.00-2.30 (4H, m), 2.50 (2H, q, J=7.3 Hz), 3.73 (3H, s), 3.79 (3H, s), 5.52 (1H, d, J=16.5 Hz), 5.66 (1H, d, J=16.5 Hz), 5.70 (1H, m), 6.00 (1H, d, J=16 Hz), 6.56-6.78 (4H, m), 7.18 (1H, d, J=9 Hz), 7.37-7.82 (9H, m), 7.94 (1H, d, J=8 Hz), 8.03 (1H, d, J=8 Hz).

Preparation 134

Compound (134) (596 mg) was obtained from Compound (129) in a manner similar to Preparation 130. The obtained Compound (134) was used in Preparation 139.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.07 (9H, s), 1.21 (3H, d, J=6.6 Hz), 1.35-1.50 (2H, m), 1.97-2.21 (4H, m), 3.77 (3H, s), 3.81 (3H, s), 4.24 (1H, q, J=6.6 Hz), 5.38 (1H, d, J=16.5 Hz), 5.57-5.68 (1H,

m), 5.58 (1H, d, J=16.5 Hz), 6.46-6.57 (2H, m), 6.68-6.80 (3H, m), 7.03 (1H, d, J=9.2 Hz), 7.22-7.77 (17H, m);

MS (ES+) m/e 848.16 (M+1).

Preparation 135

A solution of Compound (130) (566 mg) in a mixed solvent of methanol and dioxane (1:1 v/v 30 mL) was added 10% palladium on carbon, and the mixture was stirred at ambient temperature under hydrogen atomosphere (3 atm) for 4 hr. The catalyst was filtered off through a pad of Celite® and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (1:1) to give Compound (135) (628 mg) as a white foam. The obtained Compound (135) was used in Preparation 140.

^{1}H-NMR (500 MHz, $CDCl_3$, δ): 0.76 (3H, t, J=7.3 Hz), 1.06 (3x3H, s), 1.08-1.36 (6H, m), 1.55 (1H, dq, J=7.3, 6 Hz), 1.98-2.42 (4H, m), 3.72 (3H, s), 3.78 (3H, s), 4.06 (1H, t, J=6 Hz), 5.52 (1H, d, J=16.5 Hz), 5.65 (1H, m), 5.67 (1H, d, J=16.5 Hz), 6.59 (1H, dd, J=8, 2 Hz), 6.69 (1H, d, J=8 Hz), 6.72 (1H, d, J=2 Hz), 7.18-7.70 (18H, m), 7.77 (2H, m), 7.93 (1H, d, J=8.8 Hz), 8.63 (1H, d, J=8.3 Hz);

MS (ES+) m/e 846.

Preparation 136

Compound (136) (613 mg) was obtained from Compound (131) in a manner similar to Preparation 135. The obtained Compound (136) was used in Preparation 141.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.04 (9H, s), 1.14 (3H, d, J=6.5 Hz), 1.20-1.42 (4H, m), 2.00-2.23 (4H, m), 2.42 (2H, m), 3.72 (3H, s), 3.78 (3H, s), 4.14 (1H, m), 5.32 (1H, d, J=16.5 Hz), 5.66 (1H, d, J=16.5 Hz), 5.66 (1H, m), 6.59 (1H, m), 6.66-6.76 (2H, m), 7.19 (1H, d, J=8 Hz), 7.28-7.80 (19H, m), 7.93 (1H, d, J=8.8 Hz), 8.63 (1H, d, J=8 Hz).

Preparation 137

Compound (137) (494 mg) was obtained from Compound (132) in a manner similar to Preparation 135. The obtained Compound (137) was used in Preparation 142.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.06 (9H, s), 1.14-1.50 (6H, m), 2.00-2.22 (2H, m), 2.38 (2H, m), 3.71 (3H, s), 3.77 (3H, s), 4.06-4.16 (2H, m), 5.52 (1H, d, J=16 Hz), 5.60-5.72 (2H, m), 6.59 (1H, dd, J=8.5, 2 Hz), 6.65-6.74 (2H, m), 7.20 (1H, d, J=9 Hz), 7.30-7.80 (19H, m), 7.93 (1H, d, J=8 Hz), 8.62 (1H, d, J=8.5 Hz).

Preparation 138

Compound (138) (398 mg) was obtained from Compound (133) in a manner similar to Preparation 135. The obtained Compound (138) was used in Example 60.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.00 (3H, t, J=7 Hz), 1.14-1.52 (6H, m), 2.00-2.40 (6H, m), 3.73 (3H, s), 3.80 (3H, s), 5.53 (1H, d, J=16.5 Hz), 5.61-5.73 (2H, m), 6.60 (1H, dd, J=8, 1.5 Hz), 6.66-6.76 (2H, m), 7.17 (1H, d, J=8.5 Hz), 7.37-7.54 (5H, m), 7.60-7.71 (2H, m), 7.72-7.82 (2H, m), 7.93 (1H, d, J=8 Hz), 8.62 (1H, d, J=8 Hz).

Preparation 139

Compound (139) (414 mg) was obtained from Compound (134) in a manner similar to Preparation 135. The obtained Compound (139) was used in Preparation 143.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.07 (9H, s), 1.15 (3H, d, J=6.6 Hz), 1.22-1.42 (4H, m), 1.79-2.17 (4H, m), 2.37-2.50 (2H, m), 3.78 (3H, s), 3.81 (3H, s), 4.07-4.22 (1H, m), 5.39 (1H, d, J=16.5 Hz), 5.48-5.67 (1H, m), 5.72 (1H, d, J=16.5 Hz), 6.54-6.67 (1H, m), 6.69-6.83 (2H, m), 7.23-8.22 (18H, m);

MS (ES+) m/e 850.36 (M+1).

Preparation 140

To a stirred solution of Compound (135) (530 mg) in a mixed solvent of acetonitrile, methanol and water (14 : 3 : 3 v/v, 20mL) was added diammonium cerium nitrate (1.03 g) under ice-cooling, and the resulting mixture was stirred at ambient temperature for 1 hr. Additional diammonium cerium nitrate (350 mg) was added thereto, and the mixture was stirred for 1 hr. To this mixture were added saturated sodium hydrogen carbonate solution and ethyl acetate and the mixture was stirred vigorously for 10 min. The insoluble material was filtered off through a pad

of Celite®, and the filtrate was extracted with ethyl acetate. The organic phase was washed with water (twice) and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (ethyl acetate : chloroform 1:5 v/v) to give Compound (140) as a yellow foam (285 mg). The obtained Compound (140) was used in Example 61.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.78 (3H, t, J=7.5 Hz), 1.06 (3x3H, s), 1.14-1.44 (6H, m), 1.56 (1H, dq, J=7.5, 5.7 Hz), 2.13-2.44 (4H, m), 4.06 (1H, t, J=5.7 Hz), 5.40 (1H, br), 7.22-7.68 (18H, m), 7.84 (2x1H, d, J=8.5 Hz), 7.91 (1H, d, J=8.5 Hz);

MS (ES+) m/e 696.

Preparation 141

Compound (141) (377 mg) was obtained from Compound (136) in a manner similar to Preparation 140. The obtained Compound (141) was used in Example 62.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.04 (9H, s), 1.13 (3H, d, J=7 Hz), 1.18-1.48 (6H, m), 2.15-2.48 (4H, m), 4.13 (1H, m), 5.44 (1H, m), 7.23-7.68 (19H, m), 7.81-7.94 (3H, m).

Preparation 142

Compound (142) (219 mg) was obtained from Compound (137) in a manner similar to Preparation 140. The obtained Compound (142) was used in Example 63.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.05 (9H, s), 1.18-1.50 (6H, m), 2.12-2.46 (4H, m), 4.09 (2H, s), 5.42 (1H, br), 7.30-7.68 (18H, m), 7.80-7.94 (3H, m), 8.53 (1H, br).

Preparation 143

Compound (143) (136 mg) was obtained from Compound (139) in a manner similar to Preparation 140. The obtained Compound (143) was used in Example 64.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.07 (9H, s), 1.16 (3H, d, J=6.6 Hz), 1.21-1.54 (4H, m), 2.08-2.41 (4H, m), 2.39-2.55 (2H, m), 4.16 (1H, q, J=6.6 Hz), 5.20-5.38 (1H, m), 6.97-7.06 (1H, m), 7.20-7.64 (15H, m), 7.75-7.84 (2H, m), 9.86 (1x0.5H, s), 11.03 (1x0.2H, brs), 11.37 (1x0.3H, brs);

MS (ES+) m/e 700.31 (M+1).

Example 1

A mixture of Compound (7) (57 mg) and 10% palladium on barium sulfate (10 mg) in methanol (3 mL) was stirred under hydrogen atmosphere at ambient temperature for 2 hr. The catalyst was filtered off through the pad of Celite® and the solvent was evaporated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform:methanol = 10:1) to give Compound E1 as an orange powder (40 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.20-1.60 (6H, m), 1.95 (2H, m), 2.06 (1H, m), 2.22 (1H, m), 3.89 (3H, s), 5.40 (1H, m), 7.45 (1H, m), 7.52-7.80 (3H, m), 7.98 (1H, d, J=7, 7 Hz), 8.02-8.18 (4H, m), 8.40 (1H, dd, J=7, 7 Hz), 8.67 (1H, s), 9.19 (1H, br-d, J=8 Hz), 10.34 (1H, s), 12.62 (0.6H, s), 13.13 (0.4H, s);

MASS (ES+): m/e 489.

Example 2

Compound E2 (90 mg) was obtained from Compound (8) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26-1.60 (6H, m), 1.95 (2H, t, J=7.5 Hz), 2.08 (1H, m), 2.22 (1H, m), 5.42 (1H, m), 7.47 (1H, dd, J=7.5, 7.5 Hz), 7.60 (1H, dd, J=7.5, 7.5 Hz), 7.66-7.76 (2H, m), 8.00 (1H, d, J=7.5 Hz), 8.04 (2x1H, d, J=8.5 Hz), 8.08 (2x1H, d, J=8.5 Hz), 8.42 (1H, d, J=8.5 Hz), 8.68 (1H, br), 9.20 (1H, d, J=7 Hz), 10.35 (1H, s), 13.24 (1H, br);

MASS (ES+): m/e 475.

Example 3

Compound E3 (78 mg) was obtained from Compound (9) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.15-1.55 (6H, m), 1.84-2.08 (4H, m), 2.86 (3H, s), 4.75 (1H, m), 7.53 (1H, dd, J=7.5, 7.5 Hz), 7.66 (1H, dd, J=7.5, 7.5 Hz), 7.72-7.84 (2H, m), 7.91 (1H, br-d, J=6 Hz), 8.05 (1H, d, J=7.5 Hz), 8.45 (1H, d, J=7.5 Hz), 10.34 (1H, s);

MASS (ES+): m/e 405.

Example 4

Compound E4 (65 mg) was obtained from Compound (10) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26-1.60 (6H, m), 1.95 (2H, t, J=7 Hz), 2.10-2.32 (2H, m), 3.90 (3H, s), 5.50 (1H, m), 7.59-7.88 (4H, m), 7.94 (1H, br-d, J=9 Hz), 8.10-8.20 (2H, m), 8.28 (1H, d, J=8 Hz), 8.53-8.63 (2H, m), 9.45 (1H, br-d, J=8 Hz), 10.36 (1H, s);

MASS (ES+): m/e 489.

Example 5

Compound E5 (77 mg) was obtained from Compound (16) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.20-1.58 (6H, m), 1.94 (2H, t, J=7 Hz), 2.00 (1H, m), 2.14 (1H, m), 5.31 (1H, m), 7.28-7.74 (10.5H, m), 7.83 (0.5H, s), 7.97 (2H, d, J=7 Hz), 8.67 (1H, s), 8.92 (1H, br-d, J=6 Hz), 10.35 (1H, s), 12.34 (1H, br);

MASS (ES+): m/e 457.

Example 6

Compound E6 (34 mg) was obtained from Compound (17) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.10-1.64 (6H, m), 1.86-2.32 (4H, m), 5.40 (1H, m), 7.38-7.80 (7H, m), 7.86-8.10 (3H, m), 8.41 (1H, m), 8.69 (1H, br), 9.01 (1H, br), 10.36 (1H, br), 12.66 (0.6H, br), 13.24 (0.4H, br);

MASS (ES+): m/e 431.

Example 7

Compound E7 (98 mg) was obtained from Compound (18) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26-1.60 (6H, m), 1.95 (2H, t, J=7 Hz), 2.04-2.32 (2H, m), 2.81 (3H, d, J=4.5 Hz), 5.41 (1H, m), 7.50-7.86 (6H, m), 7.96-8.16 (3H, m), 8.45-8.68 (3H, m), 9.24 (1H, br-d, J=7 Hz), 10.36 (1H, br-s);

MASS (ES+): m/e 488.

Example 8

Compound (24) was dissolved in a small amount of dioxane, and 4N hydrogen chloride in dioxane (4 mL) was then added thereto

and the mixture was stirred at ambient temperature for 3 hr. The mixture was purified using a silica gel column ($CHCl_3$:MeOH=9:1) to give Compound E8 (173 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.59 (6H, m), 1.87-2.31 (4H, m), 5.26-5.39 (1H, m), 7.43-7.82 (6H, m), 7.90-8.02 (1H, m), 7.96 (2H, d, J=7.3 Hz), 8.67 (1H, s), 8.96 (1H, d, J=7.0 Hz), 10.33 (1H, s), 12.70 (1H, br);

MASS (ES+): m/e 449.39 (M+1).

Example 9

Compound E9 (38 mg) was obtained from Compound (30) in a manner similar to Example 8.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.20-1.57 (6H, m), 1.86-2.31 (2H, m), 1.94 (2H, t, J=7.3 Hz), 5.21-5.34 (1H, m), 7.14-7.32 (2H, m), 7.45-7.62 (3H, m), 7.95 (2H, d, J=6.6 Hz), 8.66 (1H, s), 8.96 (1H, d, J=7.3 Hz), 10.32-10.39 (0.6H, m), 12.65-12.73 (0.4H, m);

MASS (ES+): m/e 417.08 (M+1).

Example 10

Compound E10 (57.9 mg) was obtained from Compound (31) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.59 (6H, m), 1.87-2.31 (4H, m), 5.35-5.46 (1H, m), 7.40-7.78 (4H, m), 7.98 (1H, d, J=8.4 Hz), 8.28-8.49 (2H, m), 8.64-8.79 (2H, m), 9.13 (1H, s), 9.20-9.29 (1H, m), 10.37 (0.5H, s), 12.66 (0.3H, s), 13.15 (0.2H, s);

MASS (ES+): m/e 432.27 (M+1).

Example 11

Compound E11 (51 mg) was obtained from Compound (32) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.98-1.59 (6H, m), 1.87-2.32 (4H, m), 5.28-5.47 (1H, m), 7.37-7.78 (3H, m), 7.82-8.06 (3H, m), 8.31-8.48 (1H, m), 8.64-8.87 (3H, m), 9.27-9.38 (1H, m), 10.34 (0.5H, brs), 12.64 (0.3H, brs), 13.14 (0.2H, brs);

MASS (ES+): m/e 432.16 (M+1).

Example 12

Compound E12 (58 mg) was obtained from Compound (33) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.21-1.57 (6H, m), 1.87-2.30 (4H, m), 5.39-5.52 (1H, m), 7.43-7.84 (4H, m), 7.94-8.21 (3H, m), 8.27-8.52 (1H, m), 8.63-8.87 (2H, m), 9.04-9.29 (1H, m), 10.32 (0.7H, brs), 12.70 (0.2H, br), 13.19 (0.1H, br);

MASS (ES+): m/e 432.13 (M+1).

Example 13

Compound E13 (155 mg) was obtained from Compound (39) in a manner similar to Example 8.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.58 (6H, m), 1.87-2.29 (2H, m), 1.94 (2H, t, J=7.0 Hz), 5.26-5.37 (1H, m), 7.46-7.82 (6H, m), 7.92-8.22 (1H, m), 7.95 (2H, d, J=7.7 Hz), 8.32 (0.2H, s), 8.67 (1H, brs), 8.96 (1H, d, J=8.1 Hz), 10.31-10.40 (0.4H, m), 12.83 (0.4H, br);

MASS (ES+): m/e 406.14 (M+1).

Example 14

Compound E14 (48 mg) was obtained from Compound (40) in a manner similar to Example 8.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.59 (6H, m), 1.89-2.32 (2H, m), 1.94 (2H, t, J=7.3 Hz), 5.30-5.44 (1H, m), 6.73 (2H, d, J=8.8 Hz), 7.43-7.54 (1H, m), 7.56-7.66 (1H, m), 7.66-7.76 (2H, m), 7.85 (2H, d, J=8.8 Hz), 8.01 (1H, d, J=7.7 Hz), 8.43 (1H, d, J=7.7 Hz), 8.57-8.80 (2H, m), 10.34 (1H, s);

MASS (ES+): m/e 474.23 (M+1).

Example 15

Compound E15 (65.6 mg) was obtained from Compound (41) in a manner similar to Example 8.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.27-1.62 (6H, m), 1.89-2.34 (4H, m), 5.34-5.48 (1H, m), 7.04 (1H, dd, J=8.6, 7.0 Hz), 7.19 (1H, dd, J=8.4, 7.0 Hz), 7.32 (1H, s), 7.38-7.50 (2H, m), 7.52-7.76 (4H, m), 7.93-8.01 (1H, m), 8.32-8.45 (1H, m), 8.66 (1H, s), 8.91-9.01 (1H, m), 10.33 (0.7H, s), 11.61 (1H, s), 12.64 (0.2H, brs), 13.16 (0.1H, brs);

MASS (ES+): m/e 470.15 (M+1).

Example 16

Compound E16 (55 mg) was obtained from Compound (42) in a

manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.21-1.56 (6H, m), 1.92 (2H, t, J=7.0 Hz), 1.97-2.35 (2H, m), 5.37-5.52 (1H, m), 7.37-7.50 (1H, m), 7.53-7.78 (3H, m), 7.93-8.02 (1H, m), 8.27-8.46 (1H, m), 8.65 (1H, s), 8.78-8.83 (1H, m), 8.92 (1H, d, J=2.2 Hz), 9.17-9.34 (1H, m), 9.25 (1H, s), 10.32 (0.7H, brs), 12.64 (0.2H, brs), 13.12 (0.1H, brs);

MASS (ES+): m/e 433.12 (M+1).

Example 17

Compound E17 (65.3 mg) was obtained from Compound (43) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.84 (3H, t, J=6.6 Hz), 1.14-1.41 (8H, m), 1.40-1.61 (4H, m), 1.76-2.30 (6H, m), 5.06-5.22 (1H, m), 7.40-7.50 (1H, m), 7.52-7.76 (3H, m), 7.92-8.02 (1H, m), 8.29-8.46 (2H, m), 8.67 (1H, s), 10.34 (0.5H, s), 12.53 (0.3H, s), 13.05 (0.2H, s);

MASS (ES+): m/e 425.17 (M+1).

Example 18

Compound E18 (65.0 mg) was obtained from Compound (44) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.19-1.41 (4H, m), 1.41-1.57 (2H, m), 1.76-2.16 (4H, m), 1.92 (3H, s), 4.98-5.19 (1H, m), 7.38-7.50 (1H, m), 7.50-7.76 (3H, m), 7.91-8.02 (1H, m), 8.30-8.53 (2H, m), 8.67 (1H, s), 10.33 (0.5H, s), 12.54 (0.3H, s), 13.06 (0.2H, s);

MASS (ES+): m/e 369.12 (M+1).

Example 19

Compound E19 (77 mg) was obtained from Compound (45) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.19-1.54 (6H, m), 1.78-2.07 (4H, m), 5.02-5.16 (1H, m), 6.74-6.86 (1H, m), 6.89 (1H, dd, J=7.0, 7.0 Hz), 7.22 (2H, dd, J=8.1, 7.0 Hz), 7.40 (2H, d, J=8.1 Hz), 7.42-7.51 (1H, m), 7.54-7.77 (3H, m), 7.98 (1H, dd, J=7.7, 7.0 Hz), 8.29-8.45 (1H, m), 8.65 (1H, s), 10.32 (0.7H, brs), 12.69 (0.2H, brs), 13.18 (0.1H, brs);

MASS (ES+): m/e 446.17 (M+1).

Example 20

Compound E20 (48 mg) was obtained from Compound (46) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.07-1.52 (12H, m), 1.56-1.82 (4H, m), 1.83-2.12 (3H, m), 2.17-2.35 (1H, m), 5.06-5.20 (1H, m), 7.46-7.57 (1H, m), 7.59-7.82 (3H, m), 8.04 (1H, d, J=8.0 Hz), 8.30-8.48 (2H, m), 10.34 (1H, s);

MASS (ES+): m/e 437.14 (M+1).

Example 21

Compound E21 (96 mg) was obtained from Compound (47) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.83 (3H, t, J=6.6 Hz), 1.12-1.41 (10H, m), 1.41-1.61 (4H, m), 1.78-2.10 (4H, m), 2.08-2.29 (2H, m), 5.07-5.23 (1H, m), 7.41-7.50 (1H, m), 7.53-7.75 (2H, m), 7.65 (1H, s), 7.93-8.02 (1H, m), 8.32-8.44 (2H, m), 8.67 (1H, s), 10.33 (0.5H, s), 12.51 (0.3H, s), 13.06 (0.2H, s);

MASS (ES+): m/e 439.17 (M+1).

Example 22

Compound E22 (23 mg) was obtained from Compound (48) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.18-1.56 (6H, m), 1.82-2.13 (4H, m), 2.86 (6H, s), 4.97-5.10 (1H, m), 6.60-6.71 (1H, m), 7.40-7.49 (1H, m), 7.52-7.77 (2H, m), 7.65 (1H, s), 7.93-8.01 (1H, m), 8.34-8.46 (2H, m), 8.67 (1H, s), 10.35 (0.5H, s), 12.38 (0.3H, s), 12.95 (0.2H, s);

MASS (ES+): m/e 398.16 (M+1).

Example 23

Compound E23 (60.2 mg) was obtained from Compound (49) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.99 (1H, dt, J=7.0, 2.6 Hz), 1.17-1.37 (4H, m), 1.38-1.52 (2H, m), 1.69-2.04 (4H, m), 2.97-3.09 (2H, m), 4.92-5.06 (1H, m), 5.95-6.05 (1H, m), 6.36-6.47 (1H, m), 7.40-7.50 (1H, m), 7.50-7.74 (3H, m), 7.97 (1H, dd, J=8.1, 7.0 Hz), 8.29-8.43 (1H, m), 8.66 (1H, s), 10.33 (0.6H, s), 12.56 (0.3H, s), 13.09 (0.1H, s);

MASS (ES+): m/e 398.17 (M+1).

Example 24

Compound E24 (86 mg) was obtained from Compound (50) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.59 (6H, m), 1.88-2.29 (2H, m), 1.94 (2H, t, J=6.6 Hz), 2.37 (3H, s), 5.32-5.47 (1H, m), 7.30 (2H, d, J=7.7 Hz), 7.40-7.49 (1H, m), 7.52-7.79 (3H, m), 7.65 (1H, s), 7.89 (2H, d, J=7.7 Hz), 7.93-8.04 (1H, m), 8.34-8.48 (1H, m), 8.68 (1H, s), 8.82-8.96 (1H, m), 10.35 (1H, s);

MASS (ES+): m/e 445.20 (M+1).

Example 25

Compound E25 (48 mg) was obtained from Compound (51) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.91-1.20 (4H, m), 1.20-1.40 (2H, m), 1.68-1.92 (2H, m), 1.83 (2H, t, J=7.0 Hz), 4.42-4.52 (1H, m), 7.26-7.49 (4H, m), 7.52-7.84 (5H, m), 7.96 (1H, d, J=8.1 Hz), 8.24-8.49 (1H, m), 8.57-8.79 (1H, m), 10.30 (0.7H, s), 12.48 (0.2H, s), 12.97 (0.1H, s);

MASS (ES+): m/e 467.13 (M+1).

Example 26

Compound E26 (65.2 mg) was obtained from Compound (52) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.11-1.57 (9H, m), 1.74-2.14 (4H, m), 3.92-4.12 (2H, m), 4.77-4.92 (1H, m), 7.36-7.49 (1H, m), 7.51-7.73 (3H, m), 7.92-8.00 (1H, m), 8.34-8.42 (1H, m), 8.66 (1H, s), 10.33 (0.5H, s), 12.52 (0.3H, s), 13.02 (0.2H, s);

MASS (ES+): m/e 399.14 (M+1).

Example 27

Compound E27 (83.2 mg) was obtained from Compound (53) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22 (6H, d, J=7.0 Hz), 1.28-1.57 (6H, m), 1.89-2.30 (2H, m), 1.94 (2H, t, J=6.6 Hz), 2.89-3.01 (1H, m), 5.33-5.46 (1H, m), 7.35 (2H, d, J=8.4 Hz), 7.40-7.48 (1H, m), 7.52-7.69 (2H, m), 7.65 (1H, s), 7.72 (1H, d, J=8.8 Hz), 7.91 (2H, d, J=8.4 Hz), 7.93-8.01 (1H, m), 8.34-8.44 (1H, m), 8.66 (1H, s),

8.81-8.92 (1H, m), 10.33 (0.5H, s), 12.53 (0.3H, s), 13.06 (0.2H, s);

MASS (ES+): m/e 473.24 (M+1).

Example 28

Compound E28 (67 mg) was obtained from Compound (54) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.56 (6H, m), 1.90-2.41 (2H, m), 1.96 (2H, t, J=7.0 Hz), 2.35 (1H, s), 2.36 (2H, s), 5.28-5.40 (1H, m), 7.20-7.30 (2H, m), 7.29-7.39 (1H, m), 7.40-7.52 (2H, m), 7.54-7.78 (2H, m), 7.67 (1H, s), 7.73 (1H, d, J=9.9 Hz), 7.94-8.03 (1H, m), 8.35-8.45 (1H, m), 8.67 (1H, s), 8.74-8.84 (1H, m), 10.34 (0.5H, s), 12.56 (0.3H, s), 13.12 (0.2H, s);

MASS (ES+): m/e 445.23 (M+1).

Example 29

Compound E29 (102 mg) was obtained from Compound (55) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.20-1.59 (6H, m), 1.85-2.35 (4H, m), 2.37 (3H, s), 5.32-5.46 (1H, m), 7.33-7.50 (4H, m), 7.52-7.85 (3H, m), 7.65 (1H, s), 7.93-8.02 (1H, m), 8.34-8.44 (1H, m), 8.65-8.95 (1H, m), 8.66 (1H, s), 10.34 (0.5H, s), 12.56 (0.3H, s), 13.11 (0.2H, s);

MASS (ES+): m/e 445.24 (M+1).

Example 30

Compound E30 (80 mg) was obtained from Compound (56) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.17-1.41 (4H, m), 1.41-1.56 (2H, m), 1.77-1.99 (3H, m), 1.98-2.18 (1H, m), 2.09 (3H, s), 4.56 (2H, s), 5.05-5.24 (1H, m), 7.41-7.51 (1H, m), 7.53-7.81 (3H, m), 7.98 (1H, dd, J=8.1, 7.3 Hz), 8.31-8.45 (1H, m), 8.59-8.73 (1H, m), 8.67 (1H, s), 10.33 (0.5H, s), 12.59 (0.3H, s), 13.07 (0.2H, s);

MASS (ES+): m/e 427.13 (M+1).

Example 31

Compound E31 (42 mg) was obtained from Compound (58) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.19-1.40 (4H, m), 1.40-1.56 (2H, m),

1.83-2.15 (2H, m), 1.93 (2H, t, J=7.3 Hz), 3.93 (2H, s), 5.20-5.33 (1H, m), 5.62 (1H, brs), 7.47-7.56 (1H, m), 7.59-7.69 (1H, m), 7.70-7.82 (2H, m), 8.03 (1H, d, J=8.1 Hz), 8.23 (1H, d, J=8.8 Hz), 8.43 (1H, d, J=8.1 Hz), 8.55-8.78 (1H, m), 10.33 (1H, s);
MASS (ES+): m/e 385.15 (M+1).

Example 32

Compound E32 (86 mg) was obtained from Compound (59) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.16-1.40 (4H, m), 1.40-1.56 (2H, m), 1.80-2.15 (2H, m), 1.93 (2H, t, J=7.0 Hz), 3.36 (3H, s), 3.92 (2H, s), 5.15-5.30 (1H, m), 7.41-7.51 (1H, m), 7.53-7.79 (2H, m), 7.66 (1H, s), 7.93-8.04 (1H, m), 8.14-8.29 (1H, m), 8.29-8.46 (1H, m), 8.66 (1H, s), 10.33 (0.5H, s), 12.57 (0.3H, s), 13.07 (0.2H, s);
MASS (ES+): m/e 399.16 (M+1).

Example 33

Compound E33 (47 mg) was obtained from Compound (60) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.19-1.39 (4H, m), 1.39-1.55 (2H, m), 1.81-2.11 (2H, m), 1.92 (2H, t, J=6.6 Hz), 2.26 (6H, s), 2.91-3.03 (2H, m), 3.31 (1H, s), 5.15-5.28 (1H, m), 7.41-7.51 (1H, m), 7.54-7.77 (2H, m), 7.66 (1H, s), 7.93-8.02 (1H, m), 8.12-8.25 (1H, m), 8.27-8.42 (1H, m), 8.66 (1H, s), 10.33 (0.5H, s), 12.61 (0.3H, s), 13.13 (0.2H, s);
MASS (ES+): m/e 412.20 (M+1).

Example 34

Compound E34 (48 mg) was obtained from Compound (61) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.89 (6H, d, J=6.2 Hz), 1.19-1.42 (4H, m), 1.40-1.55 (2H, m), 1.68-2.08 (3H, m), 1.93 (2H, t, J=7.0 Hz), 3.68-3.86 (2H, m), 4.79-4.91 (1H, m), 7.41-7.51 (1H, m), 7.53-7.61 (1H, m), 7.61-7.78 (3H, m), 7.97 (1H, d, J=7.7 Hz), 8.39 (1H, d, J=7.7 Hz), 8.68 (1H, brs);
MASS (ES+): m/e 427.18 (M+1).

Example 35

Compound E35 (96 mg) was obtained from Compound (62) in a

manner similar to Example 1.

^{1}H-NMR (300 MHz, $CDCl_3$-CD_3OD, δ): 1.01 (3H, d, J=7.0 Hz), 1.07 (3H, d, J=7.0 Hz), 1.13-1.58 (6H, m), 1.82-2.12 (3H, m), 1.93 (2H, t, J=7.0 Hz), 5.12-5.23 (1H, m), 7.52-7.63 (1H, m), 7.65-7.91 (4H, m), 7.95 (1H, s), 8.08 (1H, d, J=7.3 Hz), 8.45-8.85 (1H, m), 8.49 (1H, d, J=7.3 Hz), 10.36 (1H, s);

MASS (ES+): m/e 397.16 (M+1).

Example 36

Compound E36 (77.4 mg) was obtained from Compound (63) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.16 (9H, s), 1.20-1.40 (4H, m), 1.41-1.56 (2H, m), 1.81-2.30 (2H, m), 1.93 (2H, t, J=6.6 Hz), 5.12-5.28 (1H, m), 7.40-7.50 (1H, m), 7.53-7.77 (3H, m), 7.80-7.90 (1H, m), 7.94-8.05 (1H, m), 8.31-8.45 (1H, m), 8.66 (1H, s), 10.34 (0.5H, s), 12.40 (0.3H, s), 13.04 (0.2H, s);

MASS (ES+): m/e 411.23 (M+1).

Example 37

Compound E37 (88.7 mg) was obtained from Compound (64) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.13-1.37 (4H, m), 1.38-1.54 (2H, m), 1.78-2.30 (2H, m), 1.93 (2H, t, J=7.3 Hz), 2.35-2.57 (2H, m), 2.85 (2H, t, J=7.3 Hz), 5.10-5.20 (1H, m), 7.10-7.30 (5H, m), 7.49-7.59 (1H, m), 7.61-7.70 (1H, m), 7.70-7.86 (1H, m), 8.04 (1H, d, J=8.4 Hz), 8.44 (1H, d, J=8.4 Hz), 8.50-8.80 (2H, m), 10.34 (1H, s);

MASS (ES+): m/e 459.19 (M+1).

Example 38

Compound E38 (88.7 mg) was obtained from Compound (65) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.16 (3H, t, J=7.0 Hz), 1.21-1.57 (6H, m), 1.81-2.14 (2H, m), 1.94 (2H, t, J=7.3 Hz), 3.30 (1H, d, J=15.4 Hz), 3.42 (1H, d, J=15.4 Hz), 4.07 (2H, q, J=7.0 Hz), 5.12-5.24 (1H, m), 7.48-7.58 (1H, m), 7.60-7.69 (1H, m), 7.69-7.87 (2H, m), 8.03 (1H, d, J=7.7 Hz), 8.42 (1H, d, J=7.7 Hz), 8.67 (1H, br), 8.76-8.86 (1H, m), 10.34 (1H, s);

MASS (ES+): m/e 441.18 (M+1).

Example 39

Compound E39 (66 mg) was obtained from Compound (66) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.09-1.36 (4H, m), 1.37-1.52 (2H, m), 1.76-2.11 (4H, m), 2.83 (6H, s), 5.04-5.17 (1H, m), 6.64 (2H, d, J=8.1 Hz), 7.09 (1H, d, J=8.1 Hz), 7.12 (1H, d, J=8.1 Hz), 7.40-7.51 (1H, m), 7.53-7.77 (3H, m), 7.93-8.03 (1H, m), 8.31-8.48 (1H, m), 8.51-8.62 (1H, m), 8.66 (1H, s), 10.32 (0.5H, s), 12.58 (0.3H, s), 13.10 (0.2H, s);

MASS (ES+): m/e 488.23 (M+1).

Example 40

Compound E40 (91 mg) was obtained from Compound (67) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.58 (6H, m), 1.85-2.34 (2H, m), 1.94 (2H, t, J=7.0 Hz), 5.22-5.40 (1H, m), 6.96 (1H, s), 7.39-7.49 (1H, m), 7.52-7.78 (3H, m), 7.74 (1H, s), 7.91-8.01 (1H, m), 8.29 (1H, s), 8.34-8.45 (1H, m), 8.63-8.74 (1H, m), 10.34 (0.5H, s), 12.60 (0.3H, s), 13.13 (0.2H, s);

MASS (ES+): m/e 421.15 (M+1).

Example 41

Compound E41 (85 mg) was obtained from Compound (68) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.20-1.43 (4H, m), 1.43-1.60 (2H, m), 1.88-2.10 (1H, m), 1.94 (2H, t, J=7.3 Hz), 2.10-2.32 (1H, m), 5.25-5.39 (1H, m), 6.65 (1H, dd, J=2.9, 1.1 Hz), 7.24 (1H, d, J=2.9 Hz), 7.39-7.50 (1H, m), 7.52-7.79 (3H, m), 7.93-8.02 (1H, m), 8.66 (1H, s), 8.76-8.90 (1H, m), 10.33 (0.7H, s), 12.59 (0.2H, s), 13.10 (0.1H, s);

MASS (ES+): m/e 421.18 (M+1).

Example 42

Compound E42 (51.5 mg) was obtained from Compound (69) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.17-1.41 (4H, m), 1.41-1.55 (2H, m), 1.76-2.33 (2H, m), 1.93 (2H, t, J=7.0 Hz), 2.94-3.53 (2H, m),

5.09-5.19 (1H, m), 7.45 (1H, dd, J=8.4, 7.7 Hz), 7.58 (1H, dd, J=8.4, 7.7 Hz), 7.62-7.76 (1H, m), 7.98 (1H, d, J=7.7 Hz), 8.39 (1H, d, J=8.4 Hz), 8.68 (1H, d, J=8.4 Hz), 10.33 (1H, s);
MASS (ES+): m/e 413.15 (M+1).

Example 43

Compound E43 (55.6 mg) was obtained from Compound (70) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.09 (3H, t, J=7.3 Hz), 1.18-1.56 (6H, m), 1.87-2.05 (2H, m), 1.92 (2H, t, J=7.3 Hz), 2.81-3.01 (2H, m), 4.62-4.75 (1H, m), 7.52 (1H, dd, J=7.7, 7.0 Hz), 7.65 (1H, dd, J=7.7, 7.0 Hz), 7.71-7.82 (2H, m), 7.85-7.97 (1H, m), 8.03 (1H, d, J=8.1 Hz), 8.42 (1H, d, J=8.1 Hz), 10.34 (1H, s);
MASS (ES+): m/e 419.16 (M+1).

Example 44

Compound E44 (58.2 mg) was obtained from Compound (71) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.62-0.73 (3H, m), 1.15-1.62 (8H, m), 1.85-2.05 (2H, m), 1.92 (2H, t, J=7.3 Hz), 2.58-2.96 (2H, m), 4.53-4.68 (1H, m), 7.41-7.51 (1H, m), 7.53-7.78 (3H, m), 7.80 (1H, d, J=8.1 Hz), 7.94-8.03 (1H, m), 8.30-8.45 (1H, m), 8.66 (1H, s), 10.33 (0.5H, s), 12.62 (0.3H, s), 13.15 (0.2H, s);
MASS (ES+): m/e 433.15 (M+1).

Example 45

Compound E45 (17 mg) was obtained from Compound (72) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.18-1.41 (4H, m), 1.40-1.55 (2H, m), 1.76-2.14 (4H, m), 2.35-2.62 (4H, m), 5.06-5.19 (1H, m), 7.40-7.51 (1H, m), 7.53-7.79 (3H, m), 7.93-8.03 (1H, m), 8.33-8.56 (1H, m), 8.45 (1H, d, J=8.8 Hz), 8.66 (1H, s), 10.33 (0.7H, s), 12.09 (1H, brs), 12.49 (0.2H, s), 12.99 (0.1H, s);
MASS (ES+): m/e 427.14 (M+1).

Example 46

Compound E46 (112 mg) was obtained from Compound (73) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22-1.59 (6H, m), 1.94 (2H, t,

J=7.7 Hz), 1.97-2.30 (2H, m), 5.28-5.43 (1H, m), 6.81 (2H, d, J=8.8 Hz), 7.44 (1H, dd, J=7.7, 7.7 Hz), 7.56 (1H, dd, J=7.7, 7.3 Hz), 7.60-7.76 (2H, m), 7.84 (2H, d, J=8.8 Hz), 7.92-8.03 (1H, m), 8.34-8.44 (1H, m), 8.61-8.72 (1H, m), 10.01 (1H, s), 10.34 (0.7H, s), 12.52 (0.2H, s), 13.07 (0.1H, s);

MASS (ES+): m/e 447.14 (M+1).

Example 47

Compound E47 (71 mg) was obtained from Compound (74) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.13-1.41 (4H, m), 1.27 (3H, s), 1.32 (3H, s), 1.40-1.57 (2H, m), 1.85-2.33 (2H, m), 1.93 (2H, t, J=7.0 Hz), 5.20-5.32 (1H, m), 7.55-7.64 (1H, m), 7.67-7.93 (3H, m), 8.09 (1H, d, J=8.8 Hz), 8.20-8.34 (1H, m), 8.48 (1H, d, J=8.8 Hz), 10.35 (1H, s);

MASS (ES+): m/e 413.14 (M+1).

Example 48

Compound E48 (45 mg) was obtained from Compound (75) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26-1.60 (6H, m), 1.94 (2H, t, J=7.3 Hz), 1.97-2.14 (1H, m), 2.14-2.33 (1H, m), 5.29-5.43 (1H, m), 7.39-7.49 (1H, m), 7.51-7.79 (3H, m), 7.99 (1H, d, J=8.1 Hz), 7.99 (1H, d, J=8.4 Hz), 8.13 (2H, d, J=8.4 Hz), 8.33-8.45 (1H, m), 8.66 (1H, s), 9.26 (1H, d, J=8.4 Hz), 10.34 (0.5H, s), 12.63 (0.3H, s), 13.12 (0.2H, s);

MASS (ES+): m/e 456.17 (M+1).

Example 49

Compound E49 (16 mg) was obtained from Compound (76) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.19-1.43 (4H, m), 1.42-1.62 (2H, m), 1.87-2.03 (2H, m), 2.16-3.03 (6H, m), 5.32-5.47 (1H, m), 7.42-7.53 (1H, m), 7.53-7.83 (3H, m), 7.92-8.07 (1H, m), 8.34-8.47 (1H, m), 8.62-8.79 (1H, m), 10.37 (1H, s);

MASS (ES+): m/e 409.13 (M+1).

Example 50

Compound E50 (35 mg) was obtained from Compound (86) in a

manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.35-1.62 (2H, m), 1.92-2.32 (4H, m), 3.46-3.60 (1H, m), 5.29-5.40 (1H, m), 5.71-5.80 (1H, m), 6.61-6.72 (1H, m), 7.28-8.18 (13H, m), 8.73-8.87 (1H, m), 8.89-9.01 (1H, m), 10.38-10.42 (0.2H, m), 10.50-10.58 (0.3H, m), 12.30-12.40 (0.5H, m);

MASS (ES+): m/e 455.11 (M+1).

Example 51

Compound E51 (14.5 mg) was obtained from Compound (91) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.21-1.56 (6H, m), 1.85-2.30 (4H, m), 5.22-5.33 (1H, m), 5.76-5.97 (2H, m), 7.13-7.24 (2H, m), 7.24-7.33 (2H, m), 7.32-7.42 (2H, m), 7.42-7.61 (5H, m), 7.95 (2H, d, J=7.0 Hz), 8.60-8.75 (1H, m), 8.87-9.05 (1H, m), 10.34 (1H, s);

MASS (ES+): m/e 487.18 (M+1).

Example 52

Compound E52 (14.7 mg) was obtained from Compound (91) as a by-product of Example 51.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.10-1.54 (6H, m), 1.88-2.22 (4H, m), 3.27 (2H, s), 3.31 (1H, s), 5.20-5.30 (1H, m), 5.39 (0.4H, s), 5.41 (0.6H, s), 7.08-7.16 (1H, m), 7.17-7.25 (1H, m), 7.26-7.43 (4H, m), 7.44-7.60 (5H, m), 7.94 (2H, d, J=7.3 Hz), 8.66 (0.4H, s), 8.80-8.91 (1H, m), 10.33 (0.3H, s), 12.18-12.31 (0.3H, m);

MASS (ES+): m/e 501.21 (M+1).

Example 53

A suspension of Compound (104) (4.5 g) in ethanol (150 mL) - 1N hydrochloric acid (25 mL) was refluxed for 90 min. The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of chloroform and methanol (50:1) to give N-[(1S)-1-(1H-benzimidazol-2-yl)-8-fluoro-7-oxooctyl]benzamide as a pale yellow amorphous solid. This solid was treated with

minimum amount of dry ethyl acetate to form a pale yellow crystal. The crystal was collected with diethyl ether to give Compound E53 as a light yellow crystal (3.98 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26-1.56 (6H, m), 1.92-2.06 (1H, m), 2.08-2.22 (1H, m), 2.40 (2H, ddd, J=7.7, 7.7, 2.2 Hz), 5.02 (2H, d, J=46.9 Hz), 5.24-5.35 (1H, m), 7.10-7.18 (2H, m), 7.40-7.60 (5H, m), 7.96 (2H, dd, J=8.4, 1.8 Hz), 8.88 (1H, brd, J=8.1 Hz), 12.2 (1H, brs);

MASS (ES+): m/e 382.3 (M+1).

Example 54

To a stirred solution of Compound (107) (249 mg) in N,N-dimethylformamide (5 mL) were added benzoic acid (112 mg), HOAT (167 mg) and WSCD (190 mg), and the resulting mixture was stirred at ambient temperature for 12 hr. The reaction mixture was diluted with ethyl acetate and washed successively with 10% hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform : ethyl acetate = 4 : 1) to give Compound E54 (286 mg). The obtained compound E54 was also used in Example 55.

^{1}H-NMR (300 MHz, DMSO-d_6, δ):1.15 (3H, t, J=7 Hz), 1.30-1.45 (4H, m), 1.52 (2H, m), 1.98 (2H, m), 2.26 (2H, t, J=7 Hz), 4.02 (2H, q, J=7 Hz), 5.39 (1H, q, J=7 Hz), 6.94 (1H, t, J=8 Hz), 7.05 (1H, t, J=8 Hz), 7.28 (1H, d, J=2 Hz), 7.34 (1H, d, J=8 Hz), 7.40-7.52 (3H, m), 7.64 (1H, d, J=8 Hz), 7.85 (1H, dd, J=2, 8 Hz), 8.03 (1H, d, J=8 Hz);

MASS: m/z 363 (M-1).

Example 55

To a stirred solution of Compound E54 (277 mg) in ethanol (3 mL) was added 1N-sodium hydroxide (0.85 mL), and the mixture was stirred at 50°C for 90 min. The mixture was concentrated, neutralized with 1N-hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The resulting solid

was triturated with ethyl acetate to give Compound E55 (220 mg). The obtained compound E55 was also used in preparation 108.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.28-1.57 (6H, m), 1.99 (2H, m), 2.18 (2H, t, J=7 Hz), 5.38 (1H, q, J=7 Hz), 6.94 (1H, t, J=8 Hz), 7.05 (1H, t, J=8 Hz), 7.28 (1H, d, J=2 Hz), 7.34 (1H, d, J=8 Hz), 7.40-7.52 (2H, m), 7.63 (1H, d, J=8 Hz), 7.85 (1H, dd, J=2, 8 Hz), 8.03 (1H, d, J=8 Hz).

Example 56

A mixture of Compound (108) (57 mg) and 10% palladium on barium sulfate (10 mg) in methanol (5 mL) was stirred at ambient temperature under hydrogen atmosphere (1 atm) for 3 hr. The catalyst was filtered off through a pad of Celite® and the filtrate was evaporated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform : methanol = 19 : 1) to give Compound E56 (35 mg).

^{1}H-NMR (300 M Hz, DMSO-d_6, δ): 1.26-1.57 (6H, m), 1.90-2.05 (4H, m), 5.38 (1H, q, J=7 Hz), 6.94 (1H, t, J=8 Hz), 7.05 (1H, t, J=8 Hz), 7.28 (1H, d, J=2 Hz), 7.34 (1H, d, J=8 Hz), 7.40-7.52 (2H, m), 7.63 (1H, d, J=8 Hz), 7.85 (1H, dd, J=2, 8 Hz), 8.53 (1H, d, J=8 Hz), 8.66 (1H, s).

Example 57

A mixture of Compound (110) (127 mg) and 1N HCl in EtOH (3 ml) was heated at 50°C for 2 hr, then partitioned between EtOAc and aqueous $NaHCO_3$. The organic layer was separated, washed with water and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on a silica gel eluting with a mixture of EtOAc and hexane (1:5) to give Compound E57 (83 mg) as an oil.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.30-1.45 (4H, m), 1.50-1.60 (2H, m), 1.90-2.05 (2H, m), 2.47 (2H, t, J=7 Hz), 2.87 (3H, s), 4.10-4.20 (1H, m), 5.10 (2H, d, J=47 Hz), 7.25 (2H, brd, J=8 Hz), 7.55-7.70 (2H,m), 7.83 (1H, d, J=8 Hz).

Example 58

Compound (116) (70 mg) was dissolved in tetrahydrofuran (1 mL), and then 1.0 M solution (0.332 mL) of tetrabutylammonium

fluoride in tetrahydrofuran was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 1 hr, and concentrated in vacuo. The residue was purified by preparative silica gel column chromatography using a mixture of chloroform / methanol (20:1) as an eluant. The amorphous residue was solidified with isopropyl ether to give Compound E58 (15 mg) as a colorless solid.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.13 (3H, d, J=7.0 Hz), 1.22-1.54 (6H, m), 1.88-2.19 (2H, m), 2.50 (2H, t, J=7.0 Hz), 3.94-4.05 (1H, m), 5.23-5.34 (1H, m), 5.27 (1H, d, J=5.5 Hz), 7.08-7.18 (2H, m), 7.41-7.60 (5H, m), 7.96 (2H, d, J=7.5 Hz), 8.88 (1H, d, J=7.5 Hz), 12.24 (1H, s);

MASS: 394$(M+1)^+$;

mp. 101-102°C.

Example 59

Compound E59 (16.2 mg) was obtained from Compound (117) in a manner similar to Example 58.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.13 (3H, d, J=7.0 Hz), 1.24-1.58 (6H, m), 1.90-2.23 (2H, m), 2.39-2.60 (2H, m), 3.94-4.05 (1H, m), 5.25 (1H, d, J=5.5 Hz), 5.28-5.39 (1H, m), 7.04 (1H, t, J=7.5 Hz), 7.09-7.24 (3H, m), 7.30 (1H, s), 7.44 (2H, d, J=7.5 Hz), 7.57 (1H, d, J=7.5 Hz), 7.63 (1H, d, J=7.5 Hz), 8.86 (1H, d, J=7.5 Hz), 11.60 (1H, s), 12.30 (1H, s).

MASS: 433$(M+1)^+$;

mp. 218-219°C.

Example 60

Compound E60 (160 mg) was obtained from Compound (138) in a manner similar to Preparation 140.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.88 (3H, t, J=7 Hz), 1.25-1.54 (6H, m), 1.97-2.46 (6H, m), 5.39 (1H, m), 7.41-7.76 (7H, m), 7.94-8.04 (3H, m), 8.39 (1H, m), 8.95 (1H, m), 12.58 (0.5H, br), 13.09 (0.5H, br).

Example 61

Compound E61 (82 mg) was obtained from Compound (140) in a manner similar to Example 58.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.81 (3H, t, J=7.3 Hz), 1.24-1.64 (8H, m), 2.06 (1H, m), 2.20 (1H, m), 2.42-2.56 (2H, m), 3.81 (1H, m), 5.20 (1H, d, J=5.5 Hz), 5.40 (1H, m), 7.40-7.77 (7H, m), 7.91-8.04 (3H, m), 8.39 (1H, dd, J=8.5, 8.5 Hz), 8.96 (1H, m), 12.57 (5/8H, s), 13.08 (3/8H, s);
MS (ES+) m/e 458.

Example 62

Compound E62 (144 mg) was obtained from Compound (141) in a manner similar to Example 58.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.22-1.58 (6H, m), 1.27 (3H, d, J=7 Hz), 2.13-2.48 (4H, m), 3.54 (1H, br), 4.10 (1H, m), 5.44 (1H, br), 7.35-8.14 (12H, m).

Example 63

Compound E63 (60 mg) was obtained from Compound (142) in a manner similar to Example 58.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26-1.56 (6H, m), 2.13 (2H, m), 2.39 (2H, m), 4.03 (2H, d, J=6 Hz), 5.04 (1H, t, J=6 Hz), 5.38 (1H, m), 7.40-8.04 (10H, m), 8.39 (1H, m), 8.96 (1H, m).

Example 64

Compound E64 (93 mg) was obtained from Compound (143) in a manner similar to Example 58.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.29 (3H, d, J=7.3 Hz), 1.38-1.78 (6H, m), 2.09-2.44 (4H, m), 3.48-3.60 (1H, m), 4.15 (1H, brs), 5.25-5.48 (1H, m), 7.15-7.24 (2H, m), 7.26-7.60 (4H, m), 7.75-7.85 (2H, m), 7.95 (1x0.5H, brs), 11.74 (1x0.3H, brs), 12.44 (1x0.2H, brs);
MS (ES+) m/e 462.07 (M+1).

The compounds obtained by the above-mentioned Preparations and Examples are listed in the following Table 2 (including Tables 2-1 to 2-18) and Table 3 (including Tables 3-1 to 3-8).

Table 2

Table 2-1

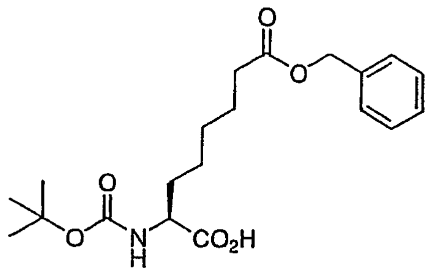
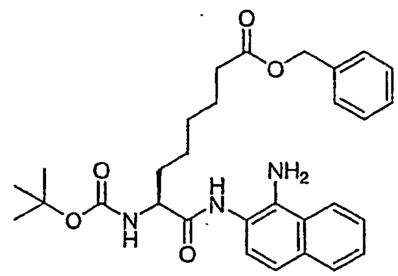
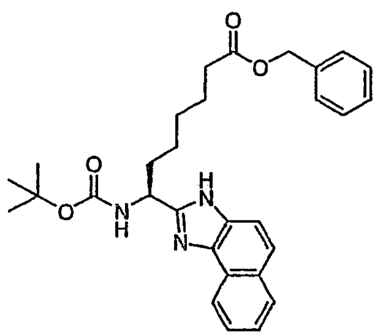
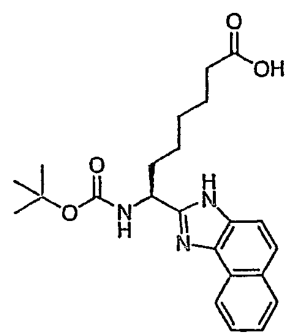
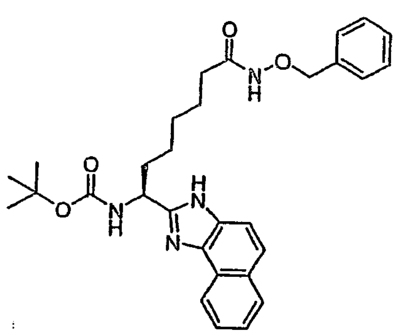
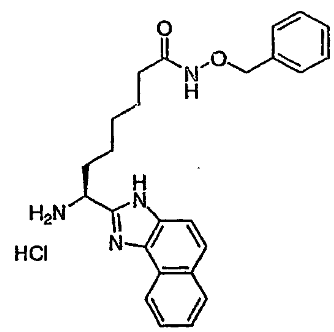
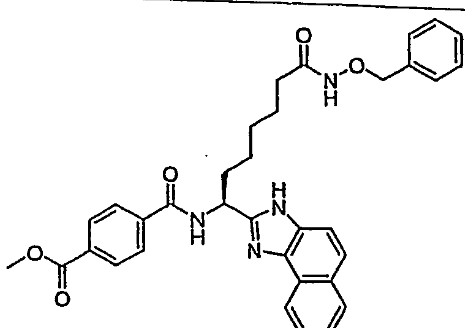
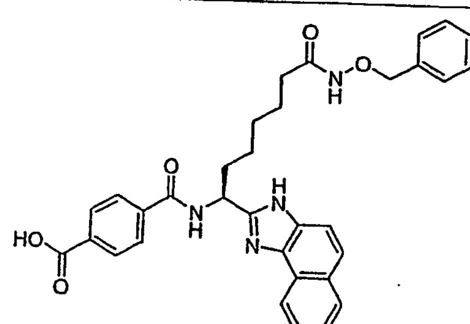
Compound (1)	Compound (2)
	
Compound (3)	Compound (4)
	
Compound (5)	Compound (6)
	
Compound (7)	Compound (8)
	

Table 2-2

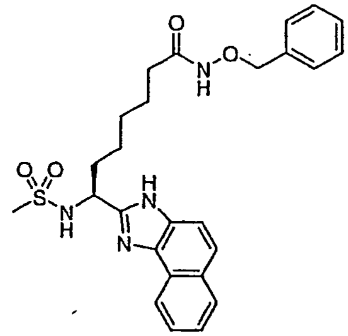
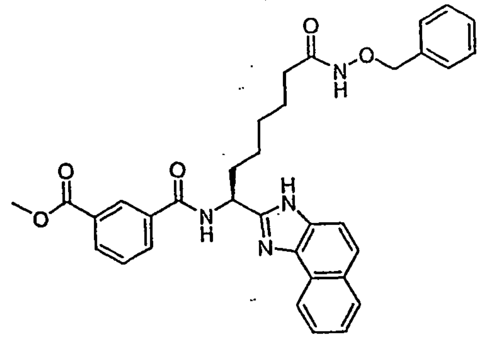
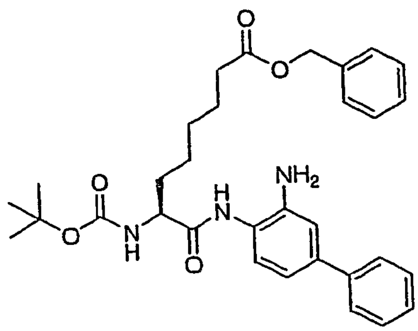
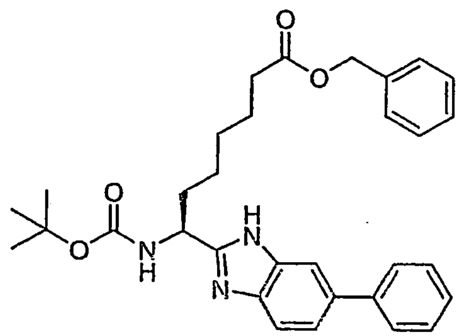
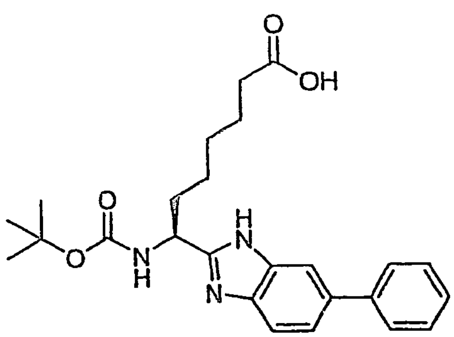
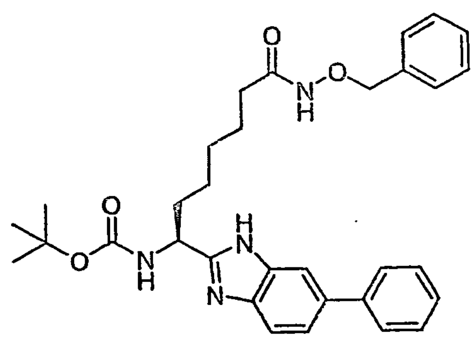
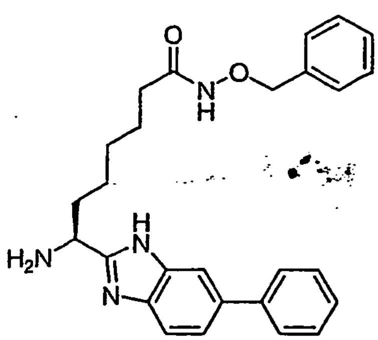
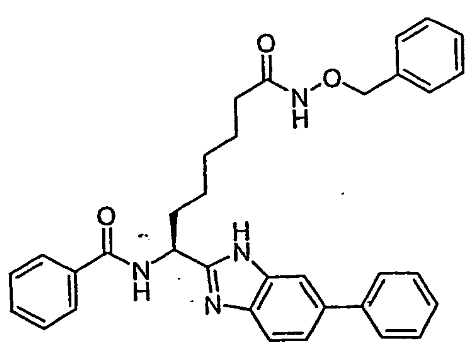
Compound (9)	Compound (10)
	
Compound (11)	Compound (12)
	
Compound (13)	Compound (14)
	
Compound (15)	Compound (16)
	

Table 2-3

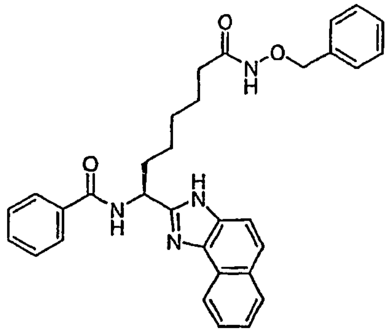
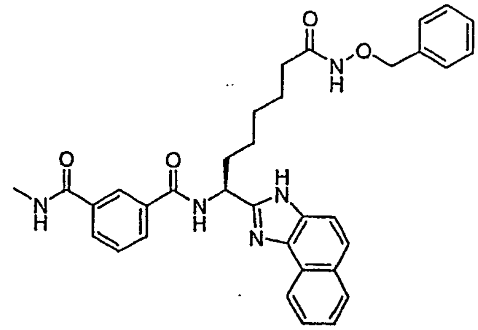
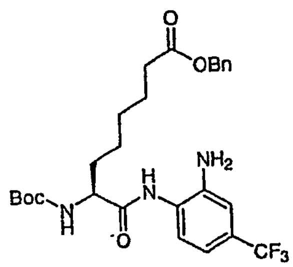
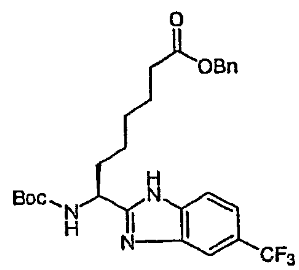
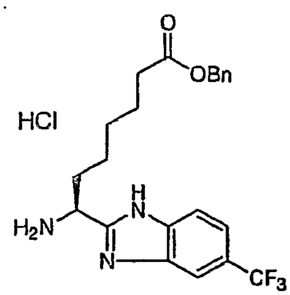
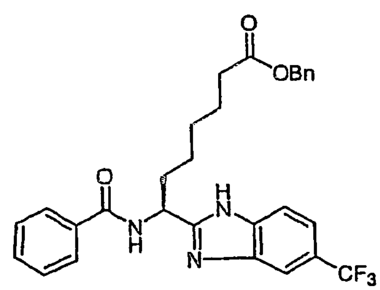
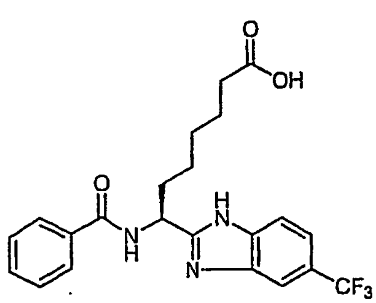
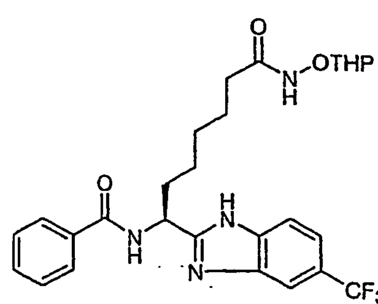
Compound (17)	Compound (18)
	
Compound (19)	Compound (20)
	
Compound (21)	Compound (22)
	
Compound (23)	Compound (24)
	

Table 2-4

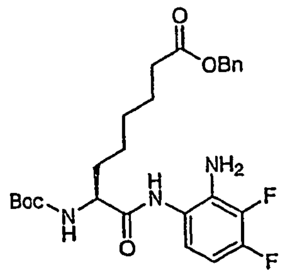
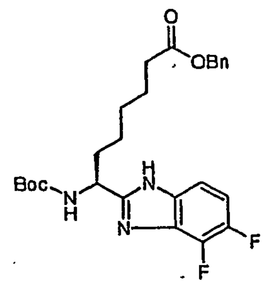
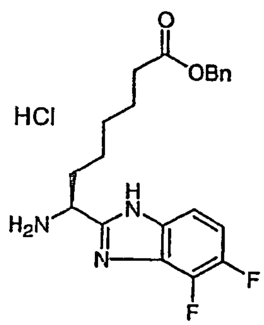
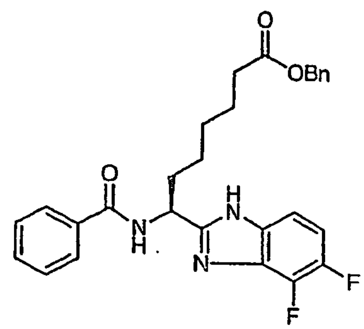
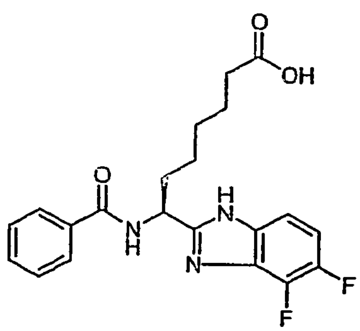
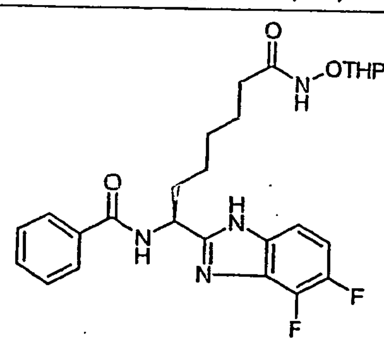
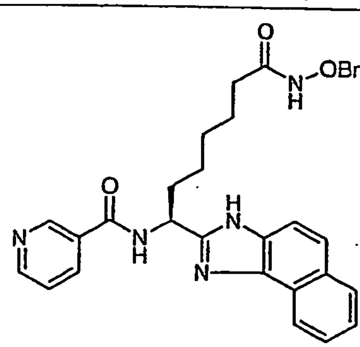
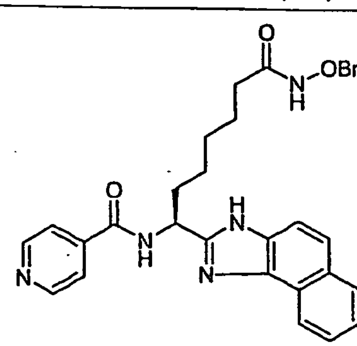
Compound (25)	Compound (26)
	
Compound (27)	Compound (28)
	
Compound (29)	Compound (30)
	
Compound (31)	Compound (32)
	

Table 2-5

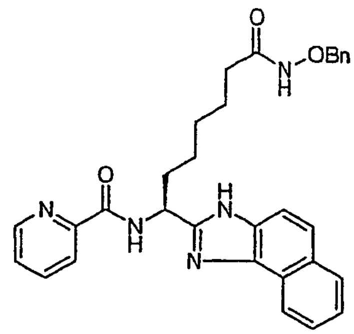
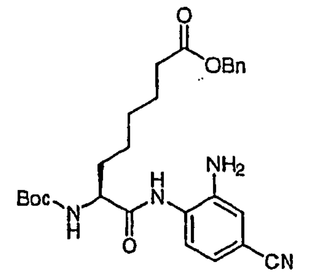
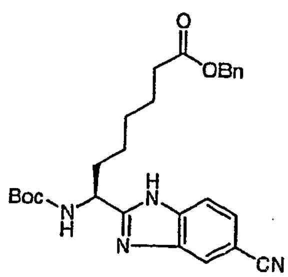
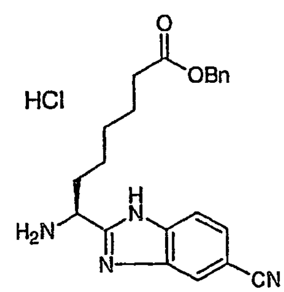
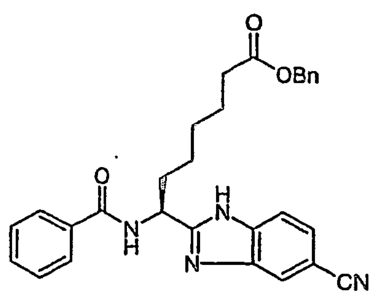
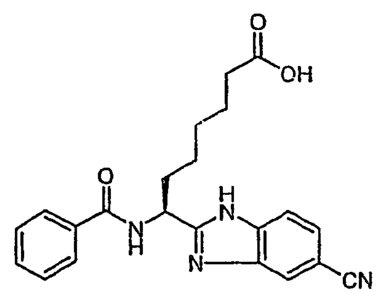
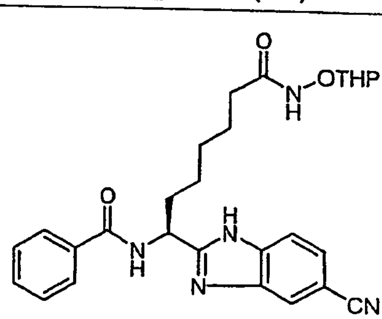
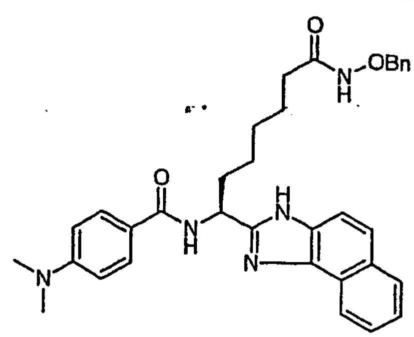
Compound (33)	Compound (34)
	
Compound (35)	Compound (36)
	
Compound (37)	Compound (38)
	
Compound (39)	Compound (40)
	

Table 2-6

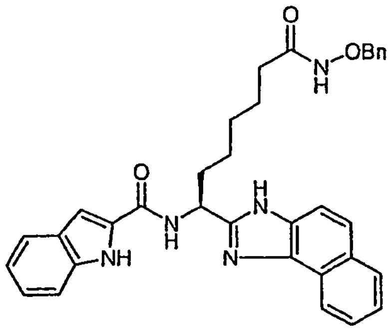
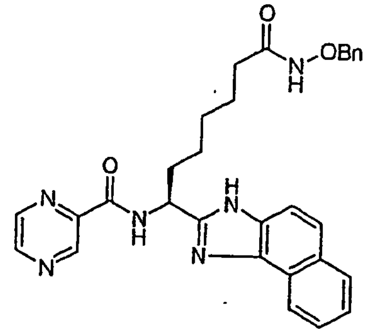
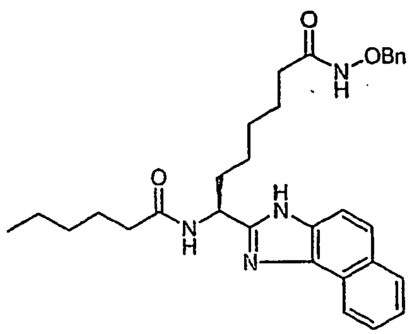
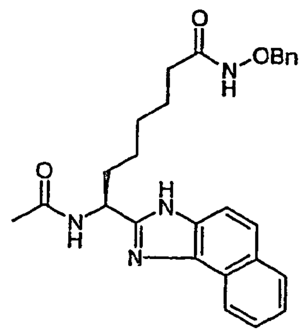
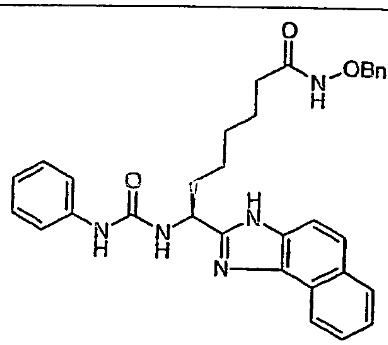
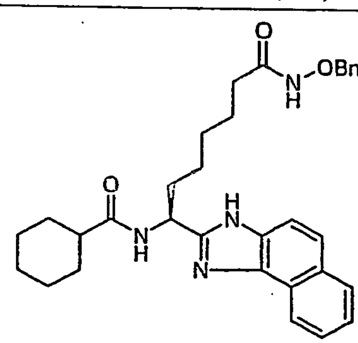
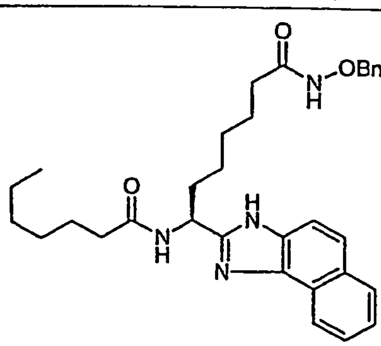
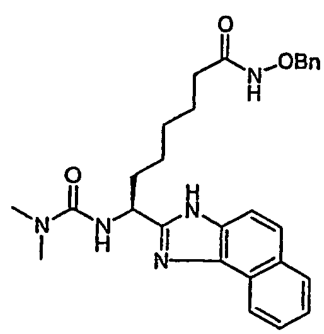
Compound (41)	Compound (42)
	
Compound (43)	Compound (44)
	
Compound (45)	Compound (46)
	
Compound (47)	Compound (48)
	

Table 2-7

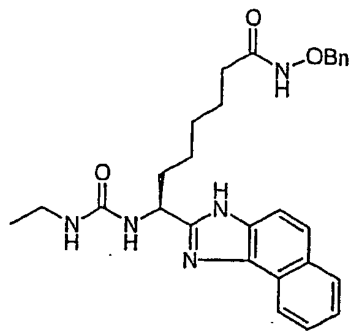
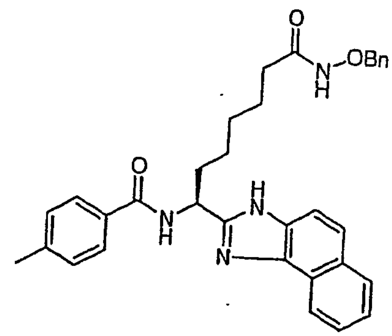
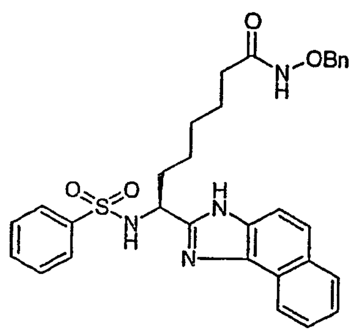
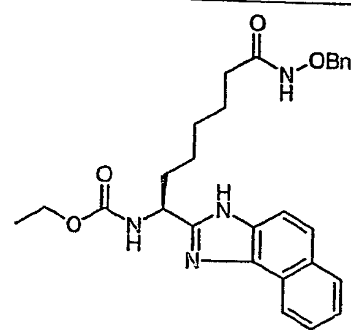
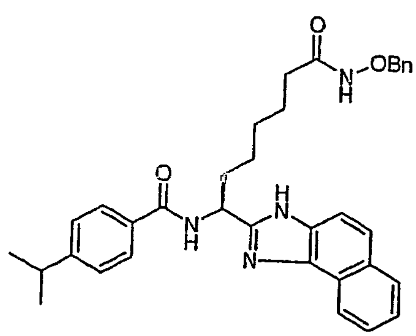
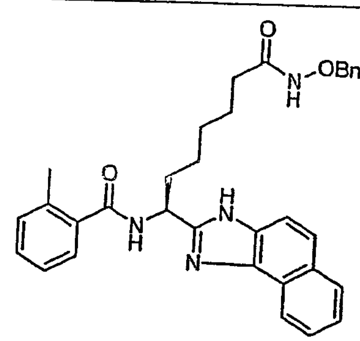
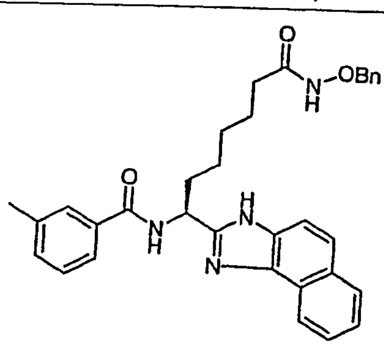
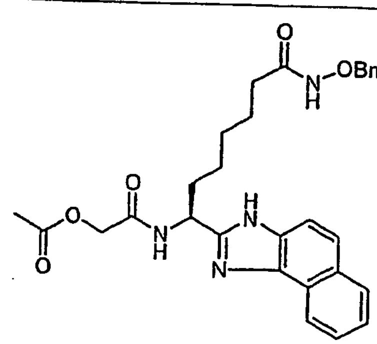
Compound (49)	Compound (50)
	
Compound (51)	Compound (52)
	
Compound (53)	Compound (54)
	
Compound (55)	Compound (56)
	

Table 2-8

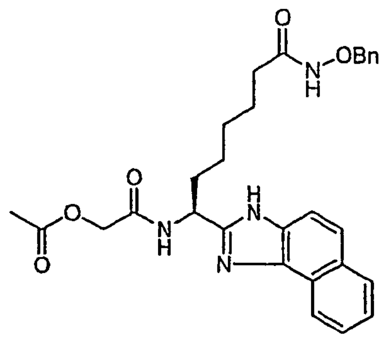
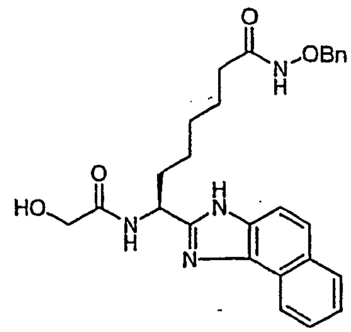
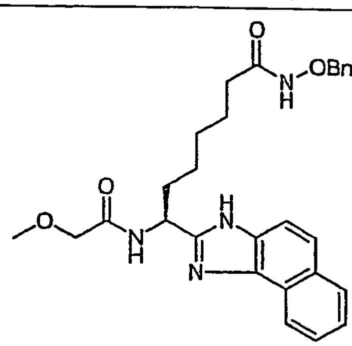
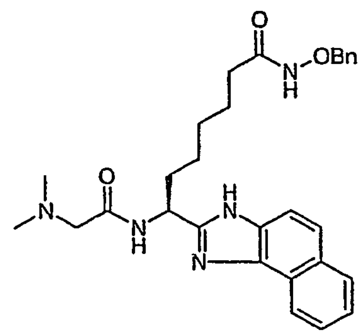
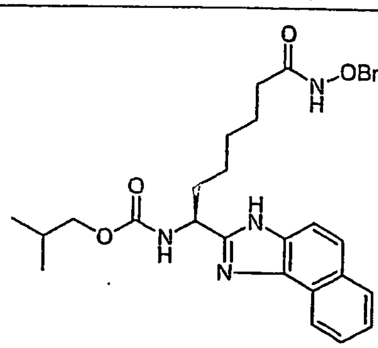
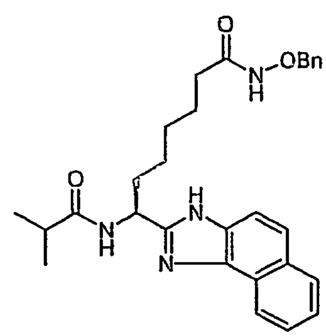
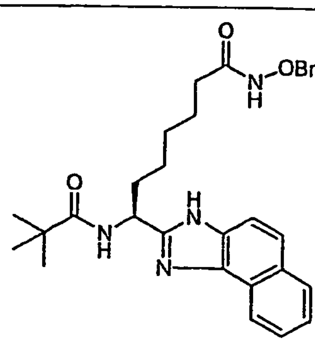
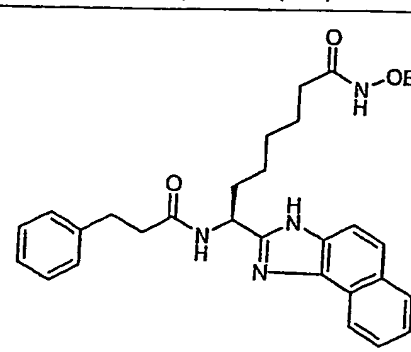
Compound (57)	Compound (58)
	
Compound (59)	Compound (60)
	
Compound (61)	Compound (62)
	
Compound (63)	Compound (64)
	

Table 2-9

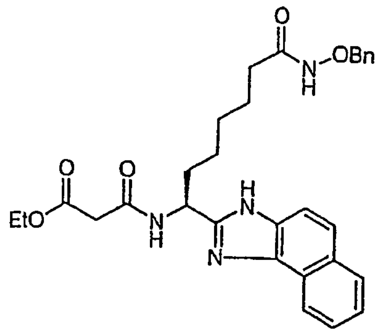
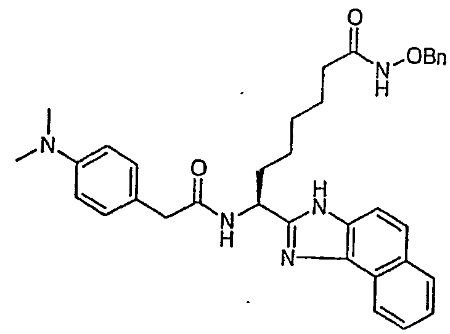
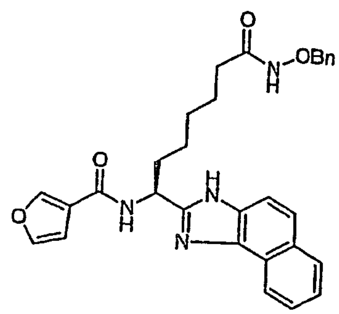
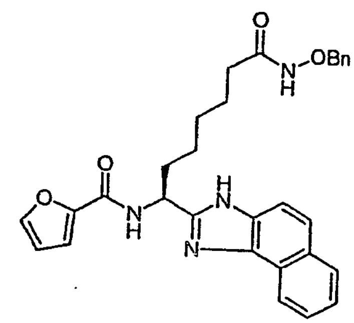
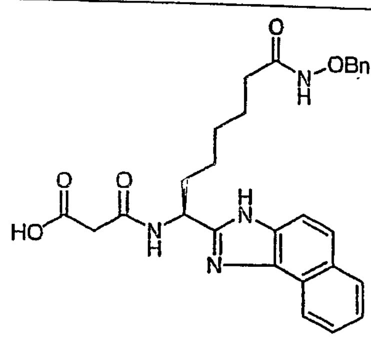
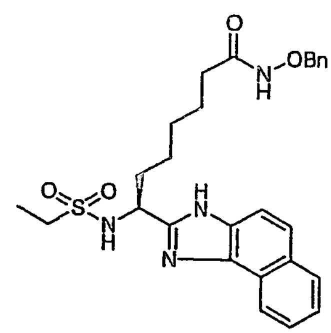
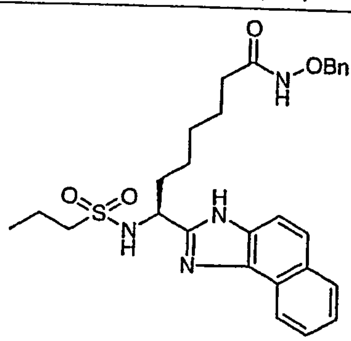
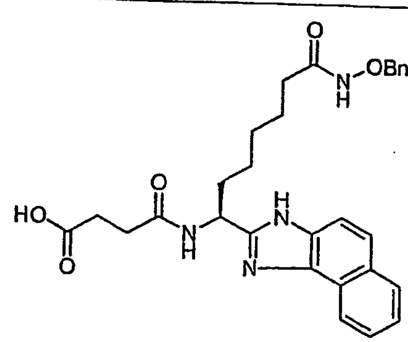
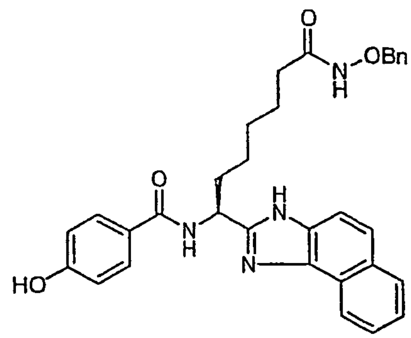
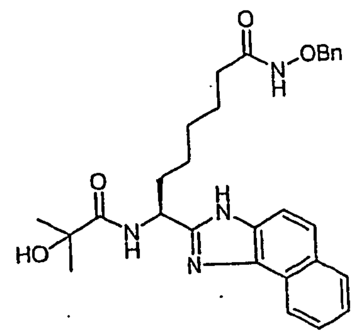
Compound (65)	Compound (66)
	
Compound (67)	Compound (68)
	
Compound (69)	Compound (70)
	
Compound (71)	Compound (72)
	

Table 2-10

Compound (73)	Compound (74)
	
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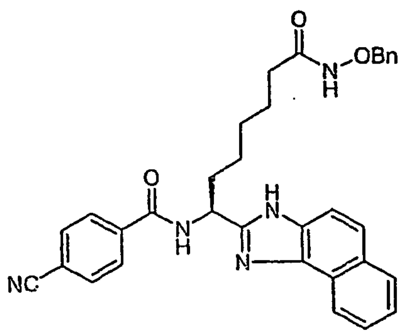
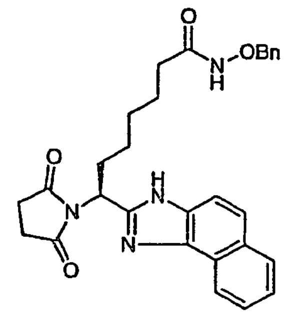
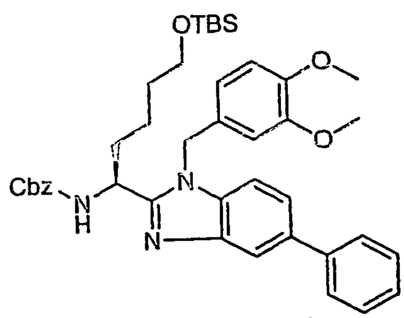
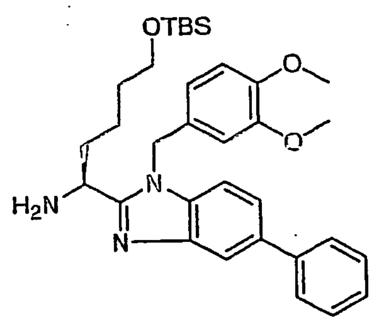
	
Compound (77)	**Compound (78)**
	
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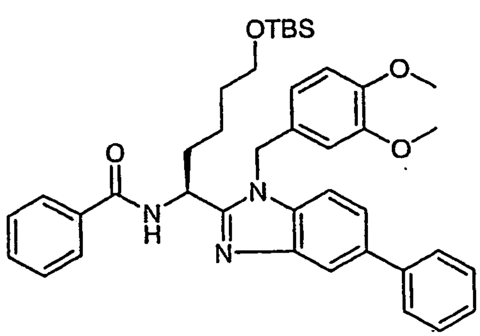	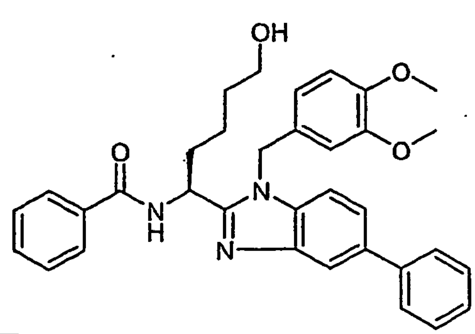

Table 2-11

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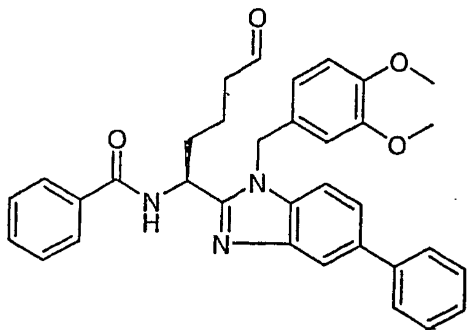	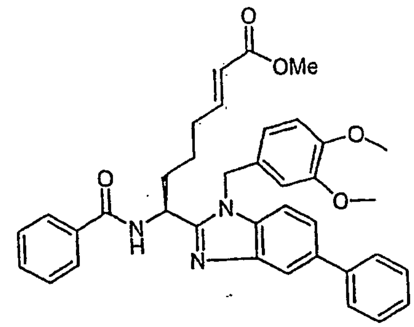
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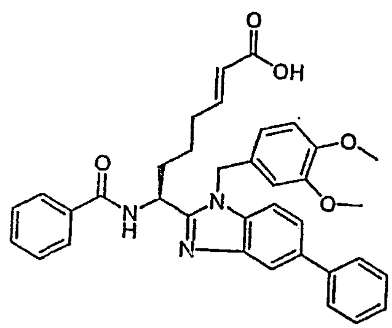	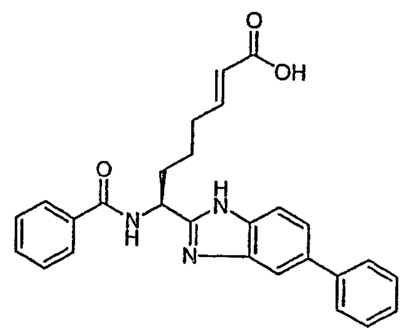
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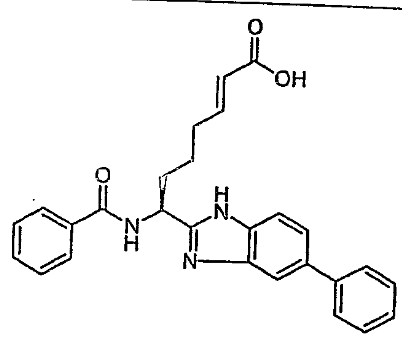	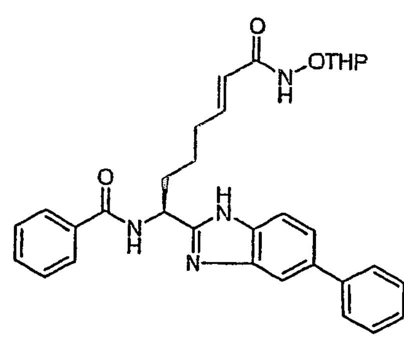
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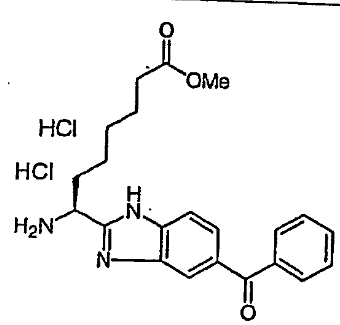	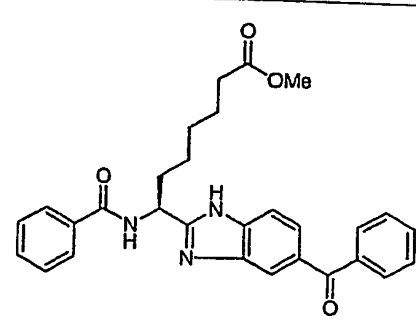

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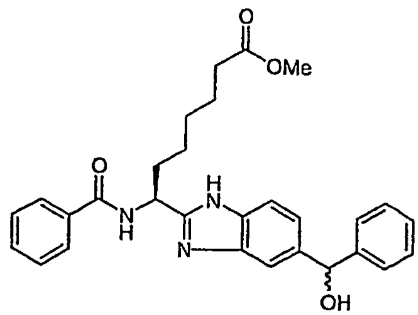
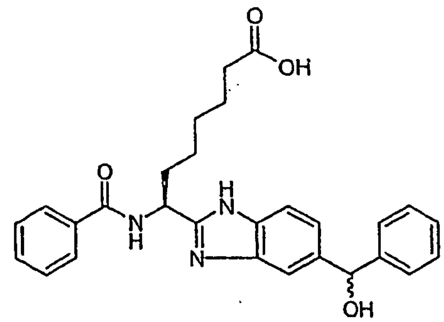
<tr><td></td><td></td></tr>
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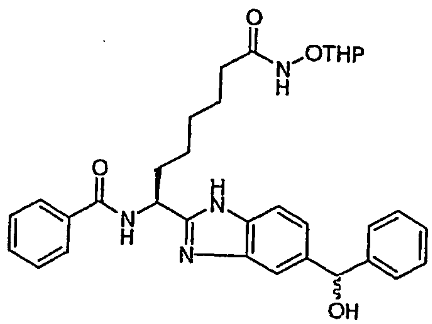
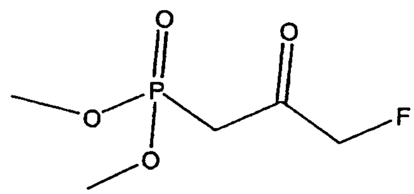
<tr><td></td><td></td></tr>
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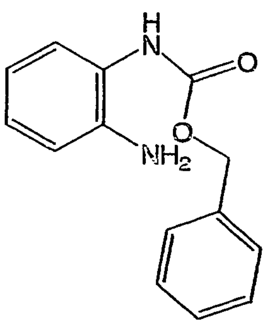
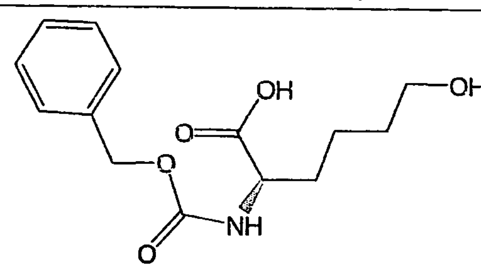
<tr><td></td><td></td></tr>
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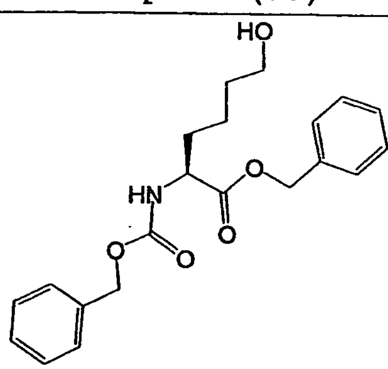
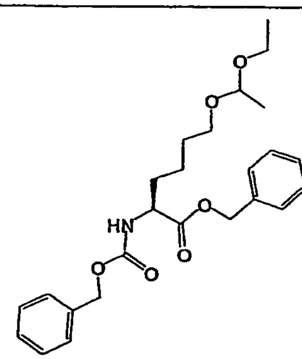
<tr><td></td><td></td></tr>
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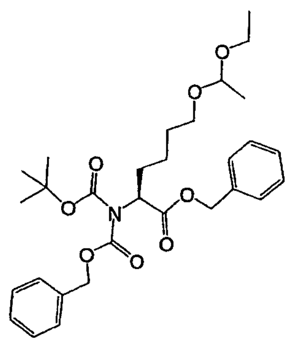	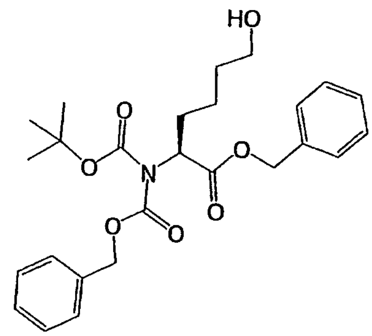
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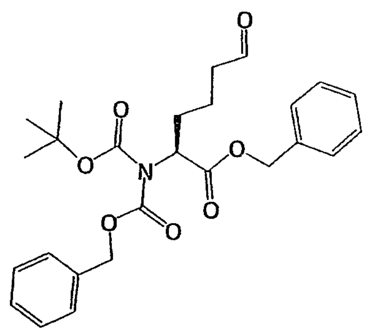	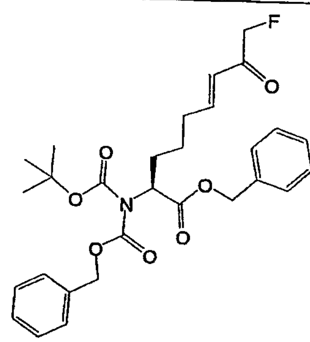
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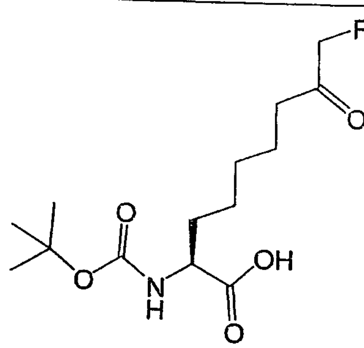	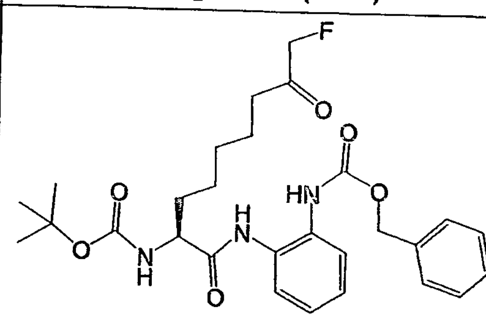
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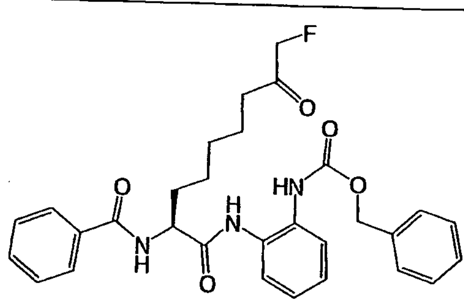	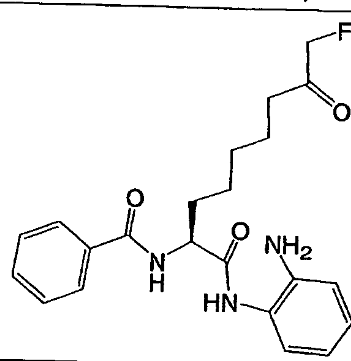

Table 2-14

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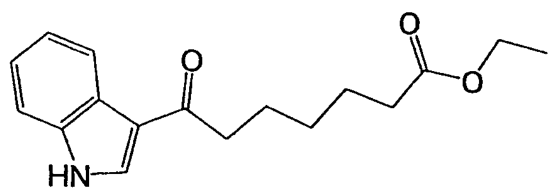	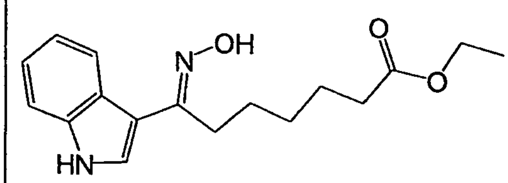
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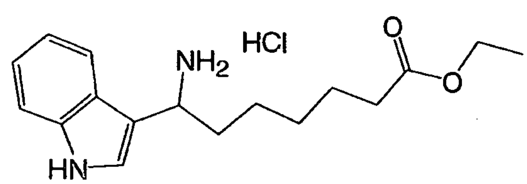	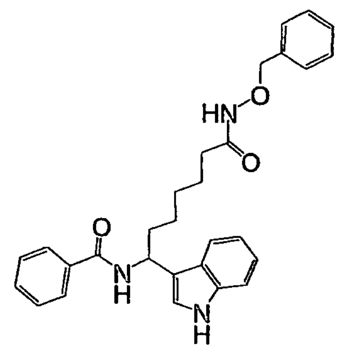
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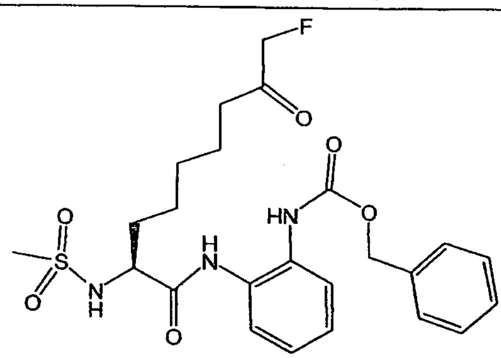	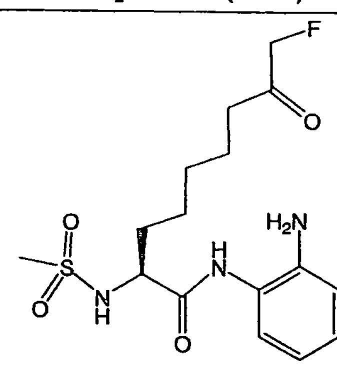
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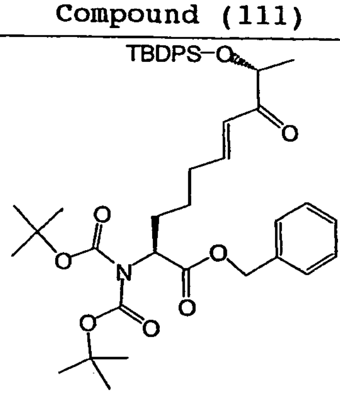	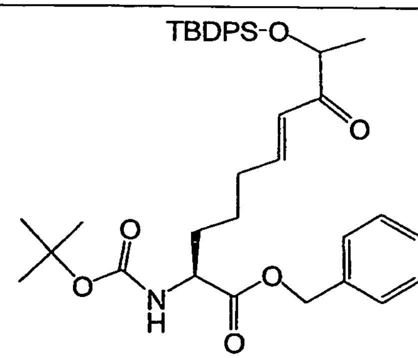

Table 2-15

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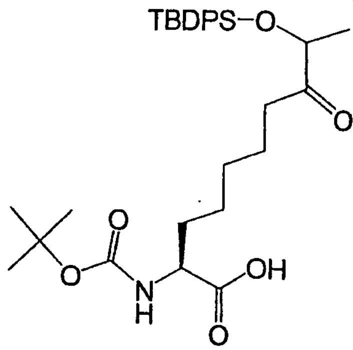	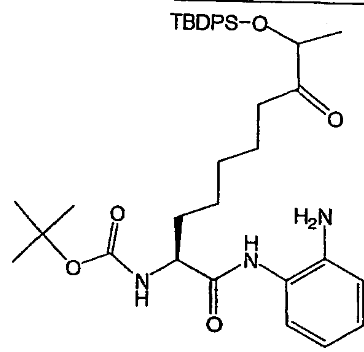
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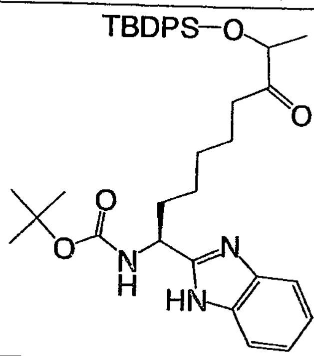	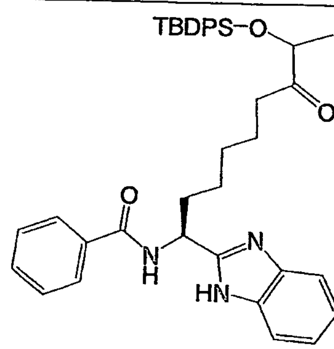
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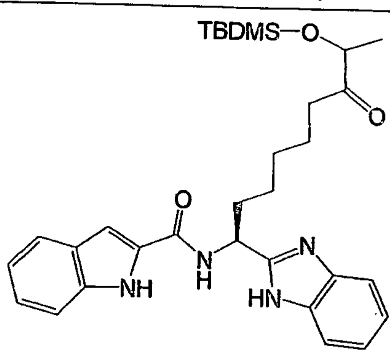	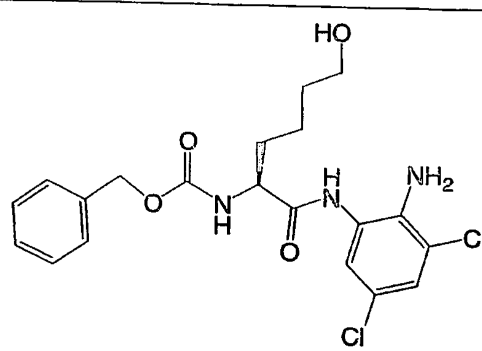
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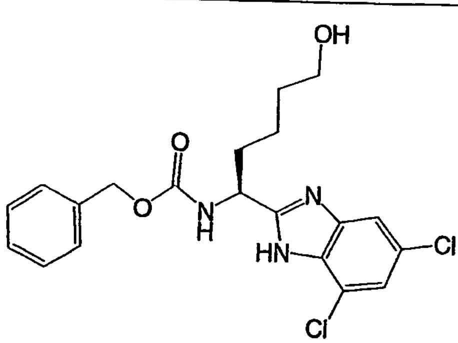	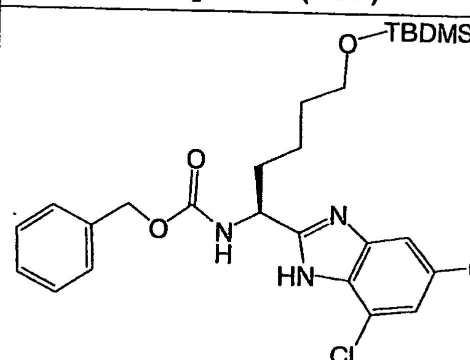

Table 2-16

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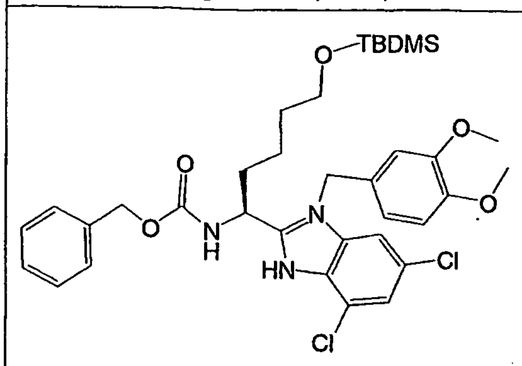	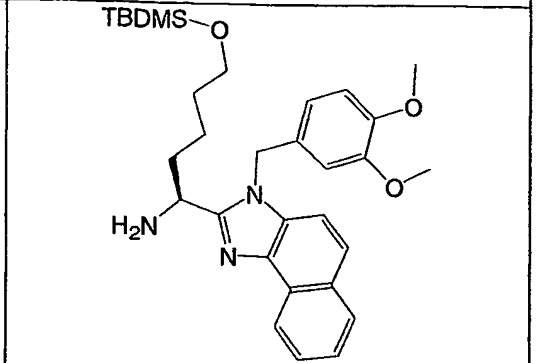
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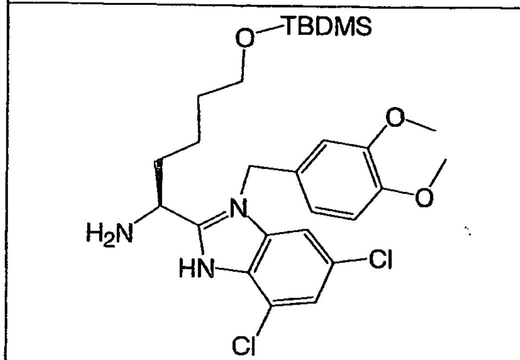	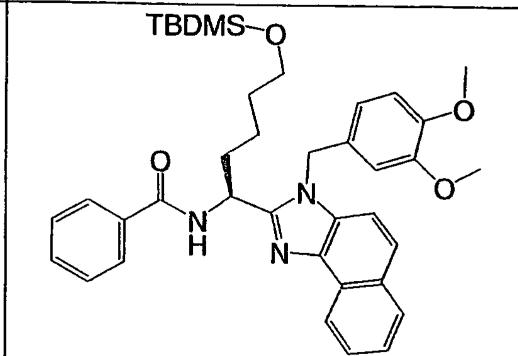
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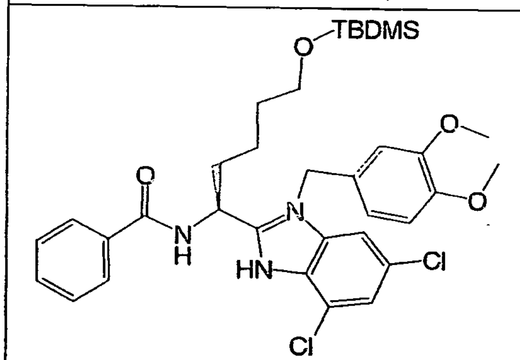	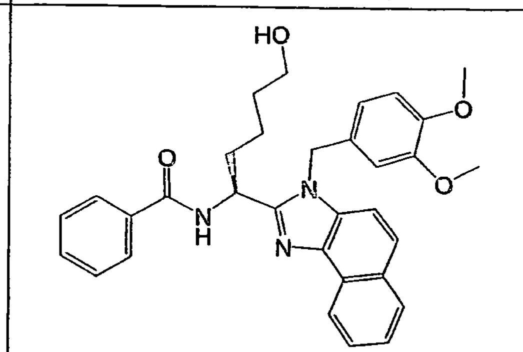
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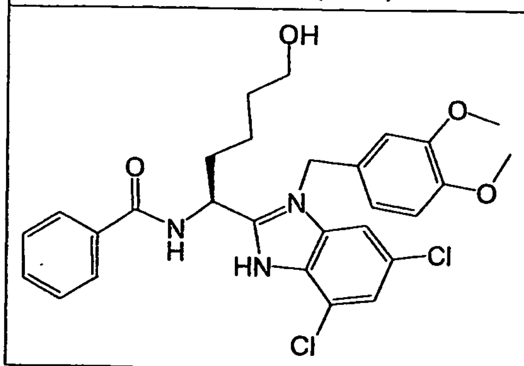
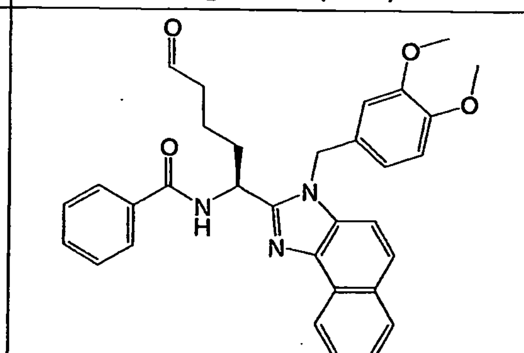
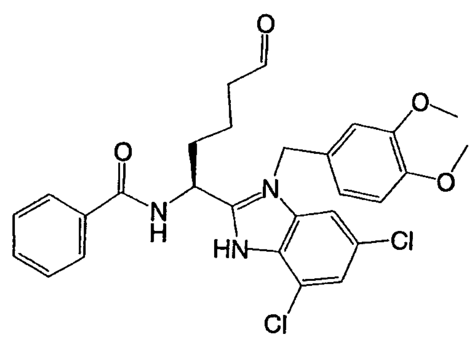
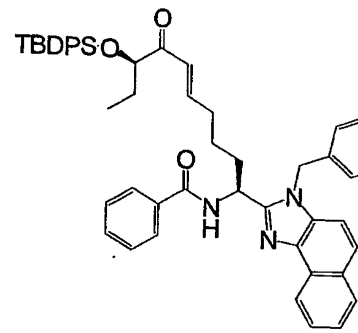
	

Table 2-17

Compound (129)	Compound (130)
	
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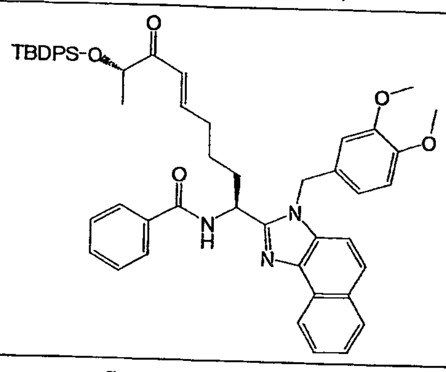	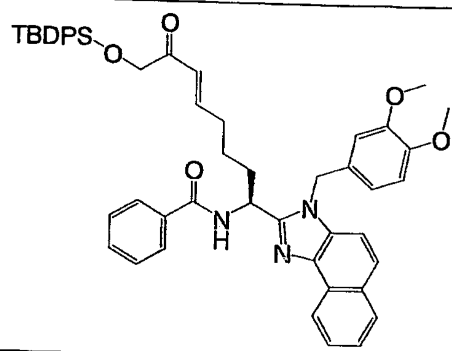
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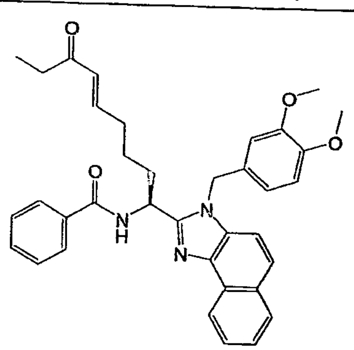	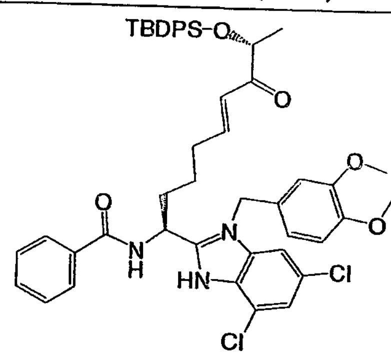
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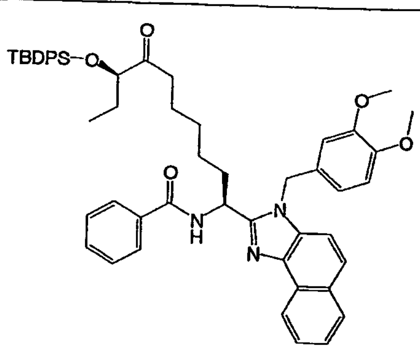	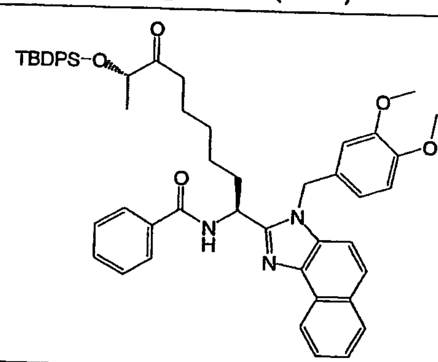

Table 2-18

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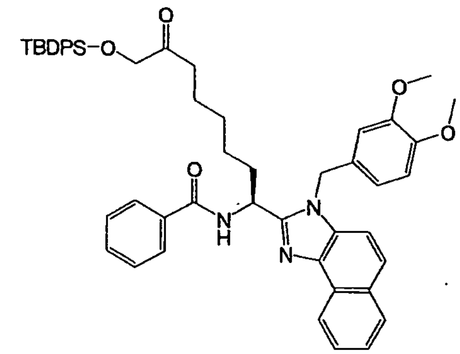
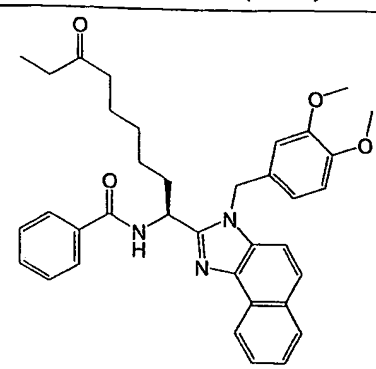
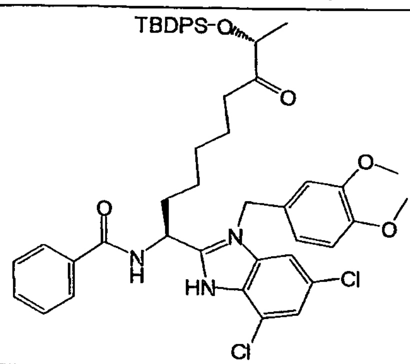
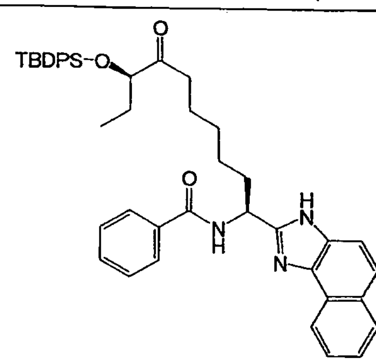
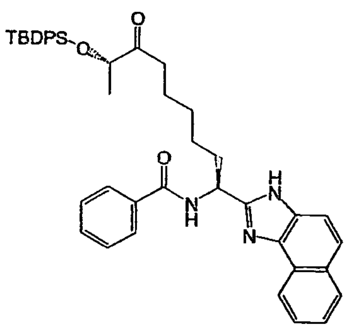
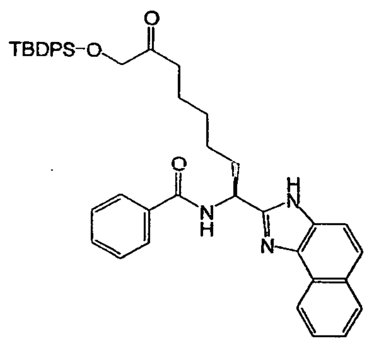
	
Compound (139)	Compound (140)
	
Compound (141)	Compound (142)
	
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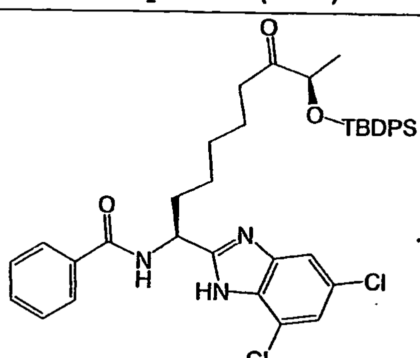
	

Table 3

Table 3-1

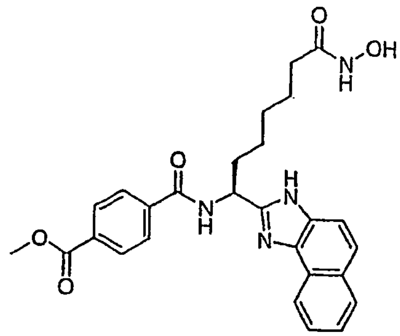
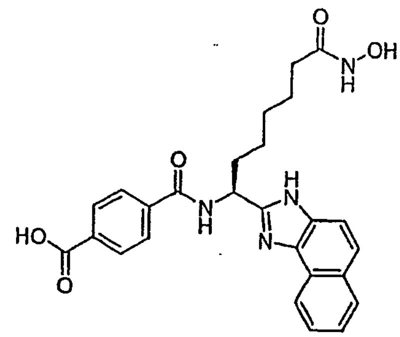
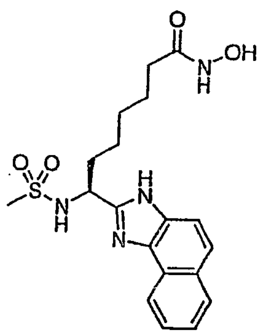
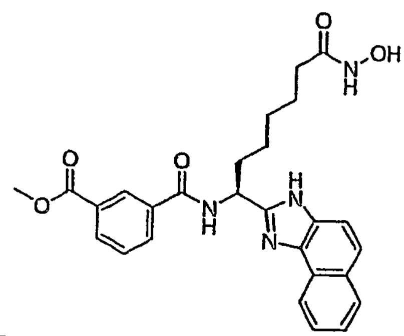
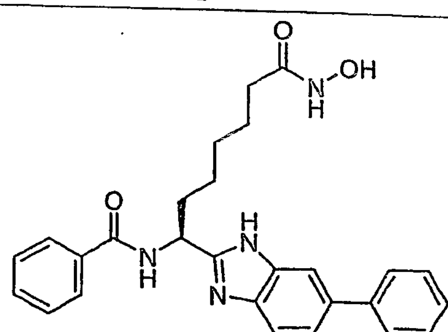
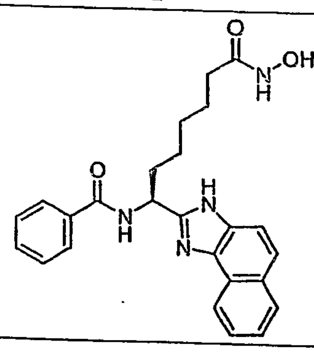
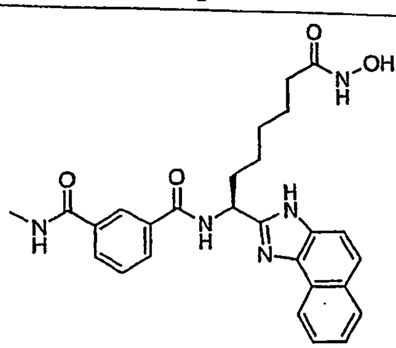
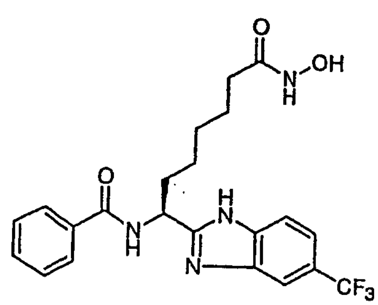
Compound E1	Compound E2
	
Compound E3	Compound E4
	
Compound E5	Compound E6
	
Compound E7	Compound E8
	

Table 3-2

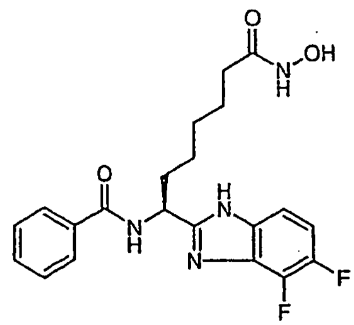
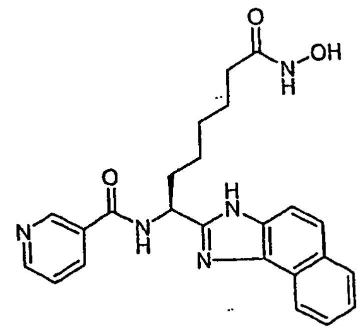
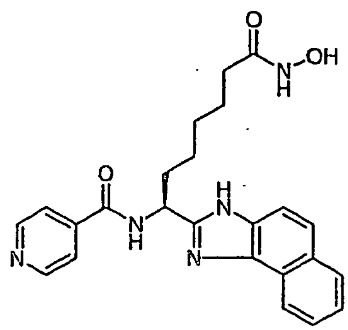
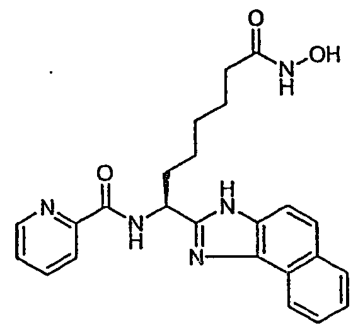
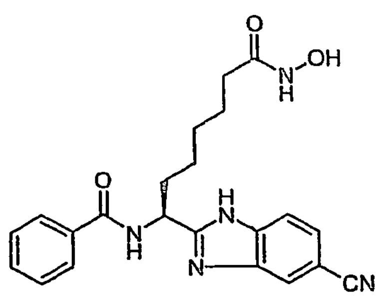
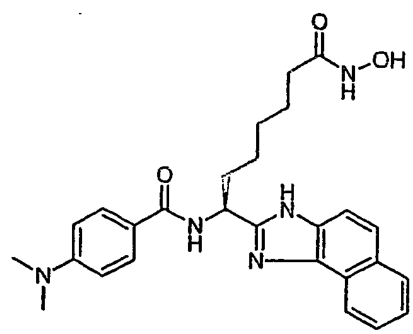
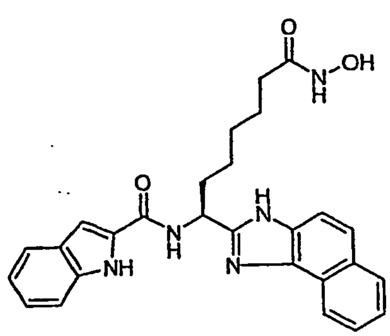
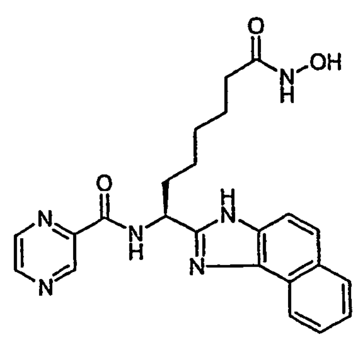
Compound E9	Compound E10
	
Compound E11	Compound E12
	
Compound E13	Compound E14
	
Compound E15	Compound E16
	

Table 3-3

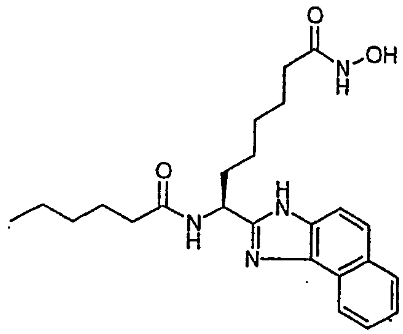
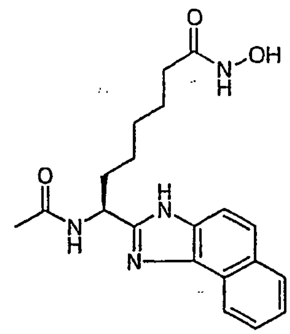
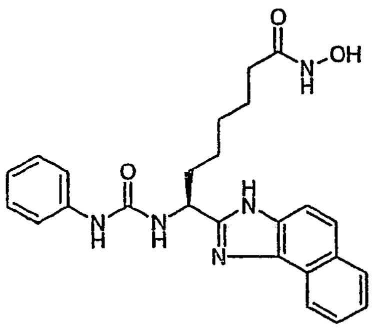
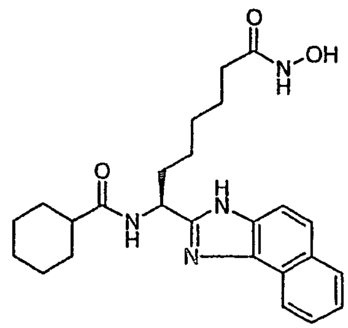
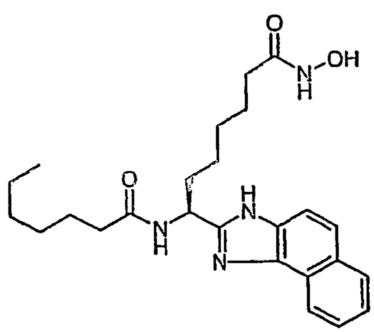
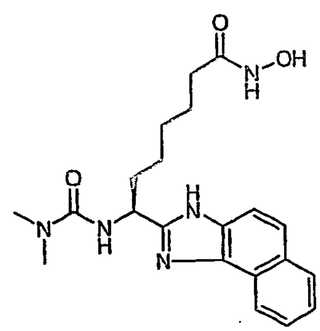
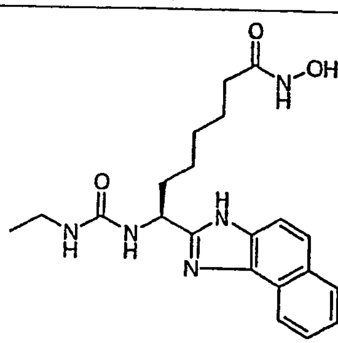
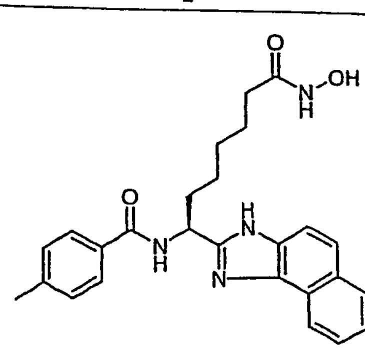
Compound E17	Compound E18
	
Compound E19	**Compound E20**
	
Compound E21	**Compound E22**
	
Compound E23	**Compound E24**
	

Table 3-4

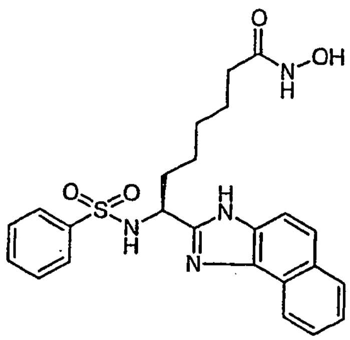
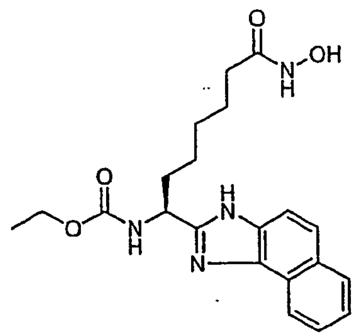
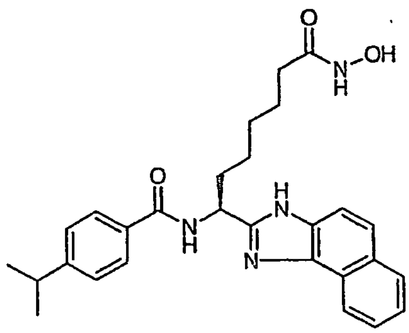
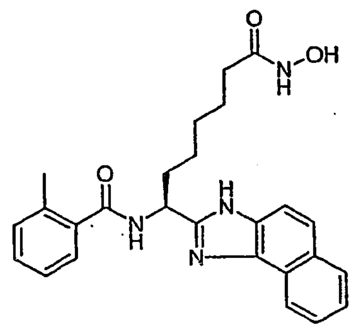
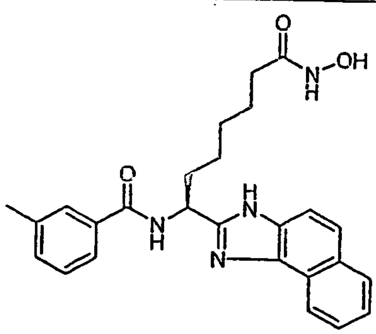
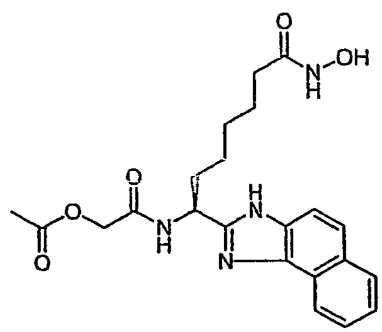
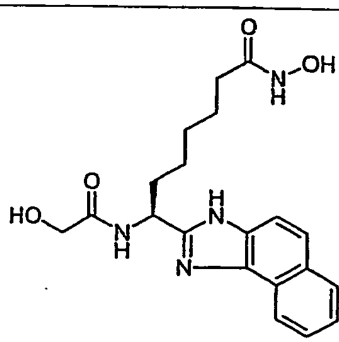
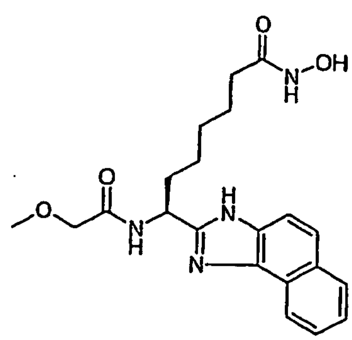
Compound E25	Compound E26
	
Compound E27	Compound E28
	
Compound E29	Compound E30
	
Compound E31	Compound E32
	

Table 3-5

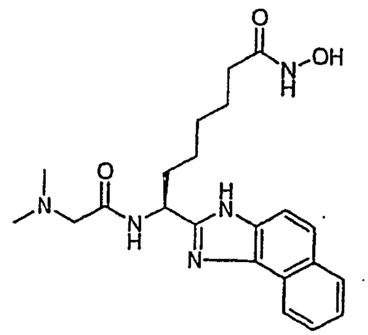
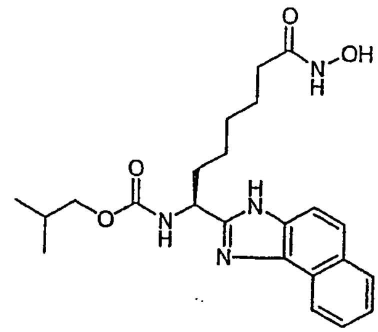
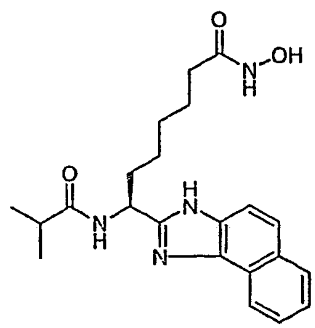
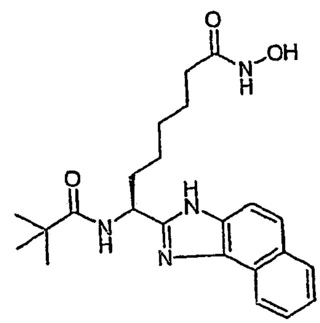
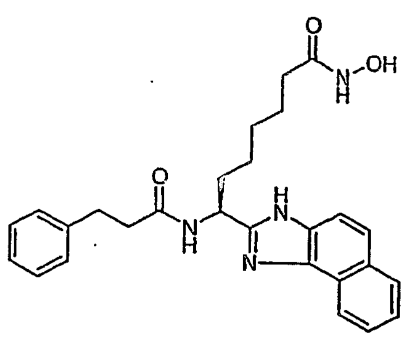
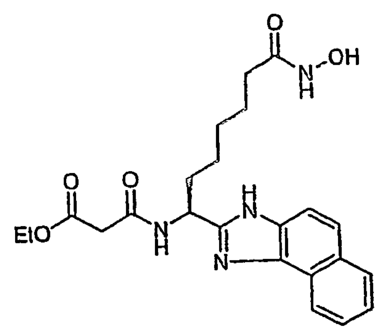
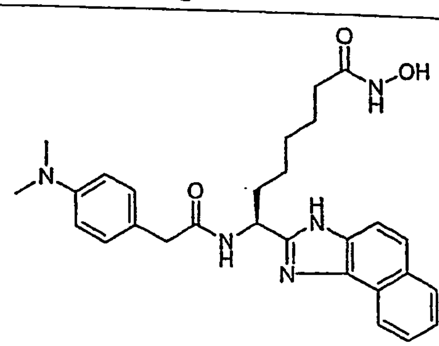
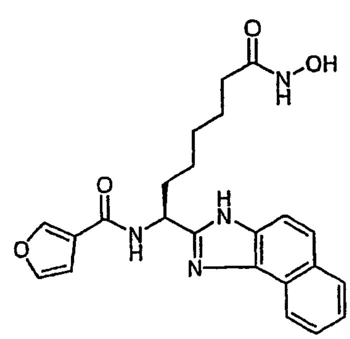
Compound E33	Compound E34
	
Compound E35	**Compound E36**
	
Compound E37	**Compound E38**
	
Compound E39	**Compound E40**
	

Table 3-6

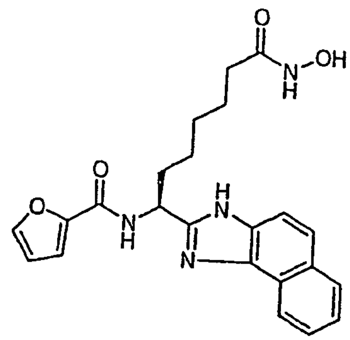
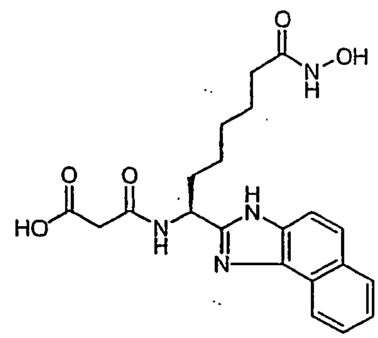
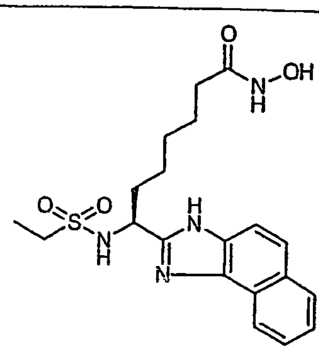
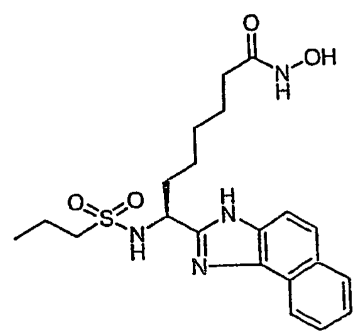
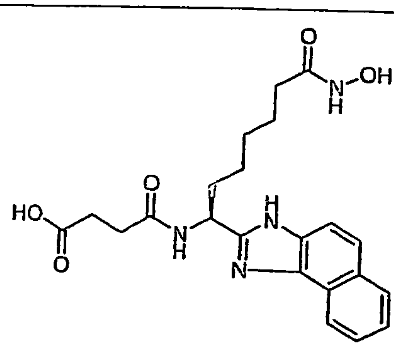
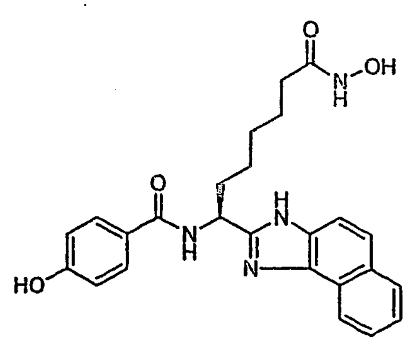
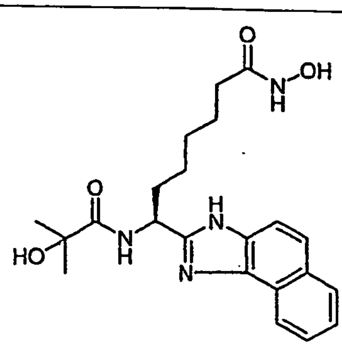
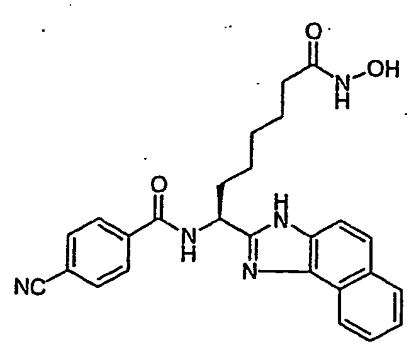
Compound E41	Compound E42
	
Compound E43	Compound E44
	
Compound E45	Compound E46
	
Compound E47	Compound E48
	

Table 3-7

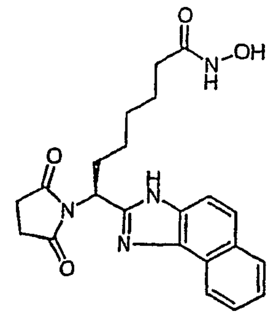
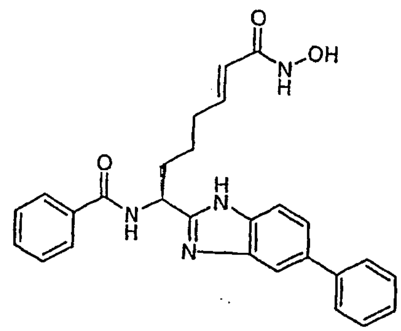
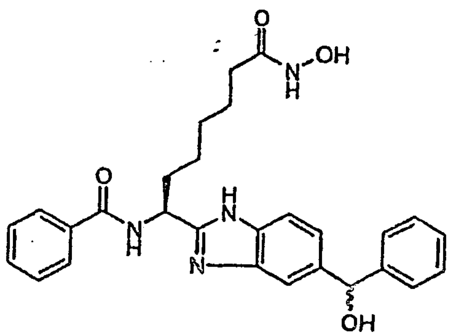
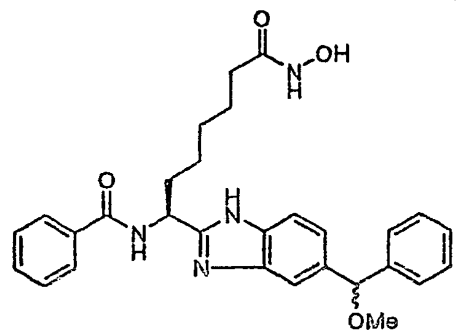
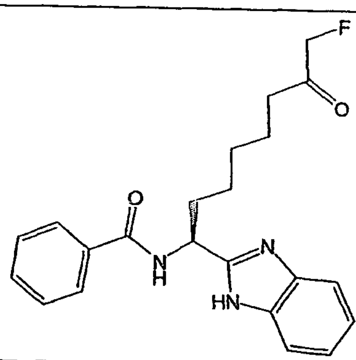
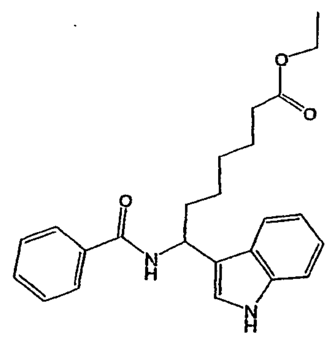
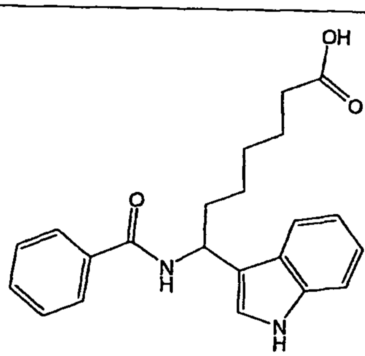
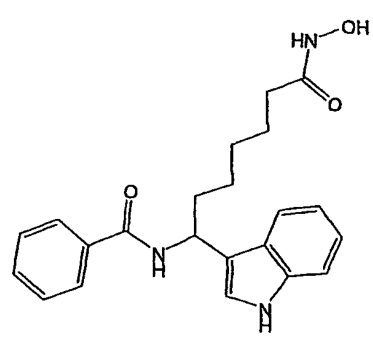
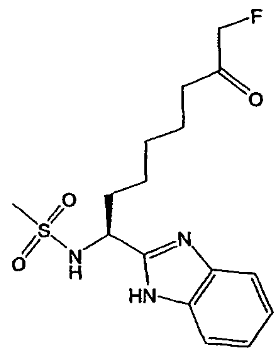
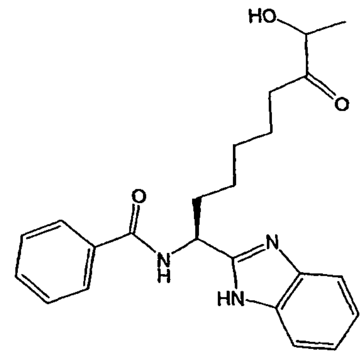
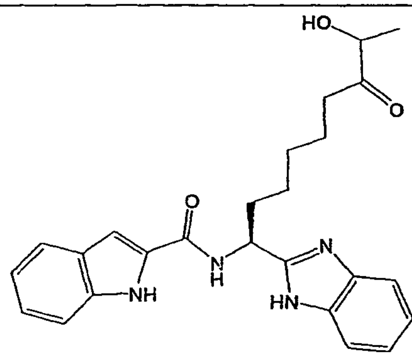
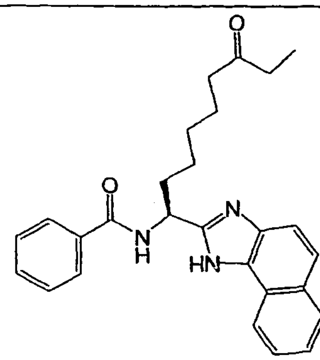
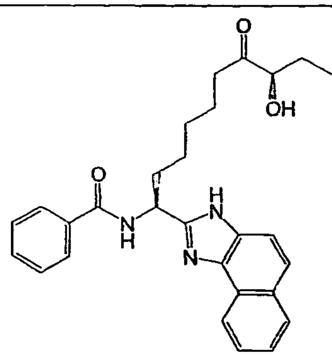
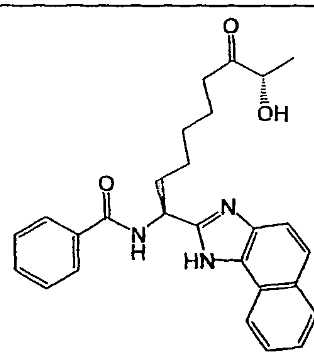
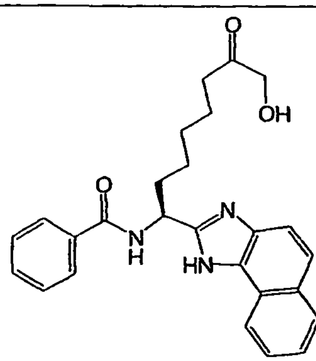
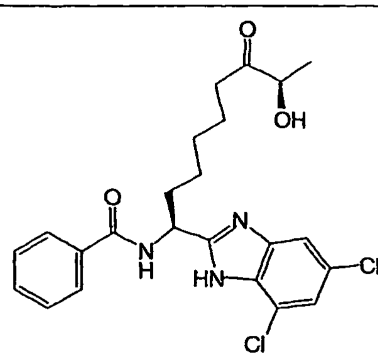
Compound E49	Compound E50
	
Compound E51	Compound E52
	
Compound E53	Compound E54
	
Compound E55	Compound E56
	

Table 3-8

Compound E57	Compound E58
	
Compound E59	Compound E60
	
Compound E61	Compound E62
	
Compound E63	Compound E64
	

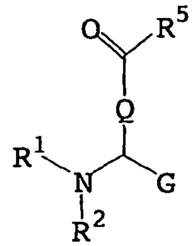
INDUSTRIAL APPLICABILITY

According to the invention, a compound having a potent inhibitory effect on the activity of histone deacetylase and a pharmaceutical composition containing said compound as an active ingredient can be provided. The compound is useful as an active ingredient of an immunosuppressant and an antitumor agent, and useful as a therapeutic or prophylactic agent for diseases such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections, tumors, etc.

This application is based on the patent application No. 2003900608 filed in Australia, and the contents of which are incorporated hereinto by reference.

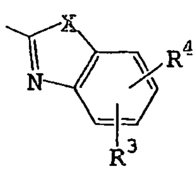
CLAIMS

1. A compound of the following formula (I):

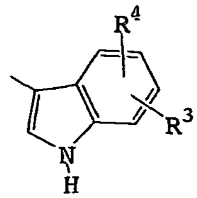


(I)

wherein
R^1 is acyl,
R^2 is hydrogen, or
R^1 and R^2 are linked together to form a heterocyclic ring,
R^5 is hydroxy, hydroxylamino, lower alkyl, lower alkoxy, halo(lower)alkyl or hydroxy(lower)alkyl,
Q is lower alkylene or lower alkenylene, and
G is a substituent selected from the following formulas



(I-a) and



(I-b)

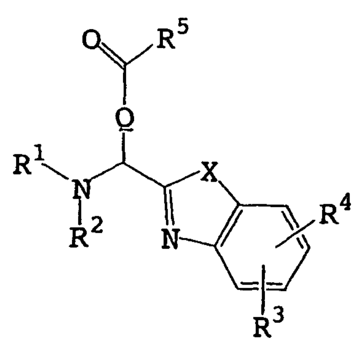
wherein
R^3 and R^4 are each independently hydrogen, halogen, halo(lower)alkyl, cyano, aryl or aryl(lower)alkyl optionally substituted with one or more suitable substituent(s), or
R^3 and R^4 are linked together to form an aromatic ring, and
X is NH, O or S,
or a salt thereof.

2. The compound of claim 1, wherein
R^1 is acyl selected from the group consisting of arylcarbonyl in which the aryl portion is optionally substituted with one or more suitable substituent(s); heterocyclic carbonyl; lower alkyl-carbonyl; carbamoyl in which the amino portion is optionally mono- or di-substituted with suitable substituent(s); lower alkyl-carbonyloxy(lower)alkylcarbonyl; lower alkoxycarbonyl;

lower alkylsulfonyl; and arylsulfonyl,
R^2 is hydrogen, or
R^1 and R^2 are linked together to form a heterocyclic ring,
R^3 and R^4 are each independently hydrogen; halogen; halo(lower)alkyl; cyano; aryl; or aryl(lower)alkyl in which the alkyl portion is optionally substituted with hydroxy or lower alkoxy, or
R^3 and R^4 are linked together to form a benzene ring,
R^5 is hydroxylamino, halo(lower)alkyl or hydroxy(lower)alkyl,
X is NH, and
Q is lower alkylene,
or a salt thereof.

3. The compound of claim 2, wherein
R^1 is arylcarbonyl in which the aryl portion is optionally substituted with one or more substituent(s) selected from the group consisting of lower alkoxycarbonyl; carboxy; lower alkylcarbamoyl; N, N-di(lower)alkylamino; lower alkyl; hydroxy; and cyano, or a heterocyclic carbonyl,
R^3 and R^4 are each independently hydrogen, or
R^3 and R^4 are linked together to form a benzene ring,
R^5 is hydroxylamino, halo(lower)alkyl or hydroxy(lower)alkyl,
X is NH, and
Q is lower alkylene,
or a salt thereof.

4. A compound of the following formula (I'):



(I')

wherein
R^1 is acyl,

R^2 is hydrogen, or
R^1 and R^2 are linked together to form a heterocyclic ring,
R^3 and R^4 are each independently hydrogen, halogen, halo(lower)alkyl, cyano, aryl or aryl(lower)alkyl optionally substituted with one or more suitable substituent(s), or
R^3 and R^4 are linked together to form an aromatic ring,
R^5 is hydroxylamino, halo(lower)alkyl or hydroxy(lower)alkyl,
X is NH, O or S, and
Q is lower alkylene or lower alkenylene,
or a salt thereof.

5. The compound of claim 4, wherein
R^1 is acyl selected from the group consisting of arylcarbonyl in which the aryl portion is optionally substituted with one or more suitable substituent(s); heterocyclic carbonyl; lower alkyl-carbonyl; carbamoyl in which the amino portion is optionally mono- or di-substituted with suitable substituent(s); lower alkyl-carbonyloxy(lower)alkylcarbonyl; lower alkoxycarbonyl; lower alkylsulfonyl; and arylsulfonyl,
R^2 is hydrogen, or
R^1 and R^2 are linked together to form a heterocyclic ring,
R^3 and R^4 are each independently hydrogen; halogen; halo(lower)alkyl; cyano; aryl; or aryl(lower)alkyl in which the alkyl portion is optionally substituted with hydroxy or lower alkoxy, or
R^3 and R^4 are linked together to form a benzene ring,
R^5 is hydroxylamino,
X is NH, and
Q is lower alkylene,
or a salt thereof.

6. The compound of claim 5, wherein
R^1 is arylcarbonyl in which the aryl portion is optionally substituted with one or more substituent(s) selected from the group consisting of lower alkoxycarbonyl; carboxy; lower alkylcarbamoyl; N, N-di(lower)alkylamino; lower alkyl; hydroxy; and cyano,
R^3 and R^4 are linked together to form a benzene ring,

R^5 is hydroxylamino,
X is NH, and
Q is lower alkylene,
or a salt thereof.

7. A histone deacetylase inhibitor comprising the compound of claim 1 or 4.

8. A method for inhibiting histone deacetylase, comprising using the compound of claim 1 or 4.

9. Use of the compound of claim 1 or 4 for the manufacture of a medicament for inhibiting histone deacetylase.

10. A pharmaceutical composition for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors, which comprises the compound of claim 1 or 4 as an active ingredient.

11. A method for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors, which comprises administering an effective amount of the compound of claim 1 or 4 to a human being or an animal.

12. Use of the compound of claim 1 or 4 for the manufacture of a medicament for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors.

13. A commercial package comprising the pharmaceutical composition of claim 10 and a written matter associated therewith, the written matter stating that the pharmaceutical composition

may or should be used for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors.

INTERNATIONAL SEARCH REPORT

PCT/JP2004/001438

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D235/02 C07D235/14 C07D235/10 C07D235/24 C07D401/12 C07D403/12 C07D405/12 C07D209/14 A61K31/405 A61K31/4184 A61P37/06 A61P35/00 A61P29/00 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BALBONI, GIANFRANCO ET AL: "Potent .delta.-Opioid Receptor Agonists Containing the Dmt-Tic Pharmacophore" JOURNAL OF MEDICINAL CHEMISTRY , 45(25), 5556-5563 CODEN: JMCMAR; ISSN: 0022-2623, 2002, XP002286789 figure 1; compound 4	1-6
X	CARDILLO, G. ET AL: "Synthesis and binding activity of endomorphin-1 analogues containing .beta.-amino acids" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 10(24), 2755-2758 CODEN: BMCLE8; ISSN: 0960-894X, 2000, XP004225343 figure 1; compound 4B	1-6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 July 2004	16/07/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schuemacher, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94/14775 A1 (SMITHKLINE BEECHAM CORP., USA) 7 July 1994 (1994-07-07) page 36, lines 9,10	1-6
X	MORALES-RIOS, MARTHA S. ET AL: "Synthesis of acetamido(indol-3-yl)propanol derivatives" HETEROCYCLES, 43(7), 1483-1496 CODEN: HTCYAM; ISSN: 0385-5414, 1996, XP001194426 compounds 5, 6	1-6
X	YANG, CHIN PING: "Reaction of phthaloylaspartic anhydride with o-phenylenediamine in solution and spectral analysis of the reaction products" JOURNAL OF HETEROCYCLIC CHEMISTRY, 19(4), 775-9 CODEN: JHTCAD; ISSN: 0022-152X, 1982, XP009033106 page 776; compound V	1-6
X	OZEGOWSKI, WERNER ET AL: "Amino acid antagonists. II. .beta.-'5(6)-Bis(.beta.-chloroethyl)-amino-2- benzimidazolyl!-DL-alanine and its derivatives as potential cytostats" JOURNAL FUER PRAKTISCHE CHEMIE (LEIPZIG), 20, 166-77 CODEN: JPCEAO; ISSN: 0021-8383, 1963, XP009033096 page 173; compound XXI	1-6
Y	WO 02/26696 A (ROMERO MARTIN MARIA ROSARIO ; FINN PAUL W (GB); HARRIS C JOHN (GB); RI) 4 April 2002 (2002-04-04) claim 176; examples 170,184,185,243-247,304-306,310	1-13
Y	US 2003/018062 A1 (REMISZEWSKI STACY W ET AL) 23 January 2003 (2003-01-23) page 1, paragraph 4; claims 1,35; examples 140,145,165-168,171,176	1-13
A	WO 02/051842 A (HOFFMANN LA ROCHE ; SAAL WOLFGANG VON DER (DE); GEORGES GUY (DE); SATT) 4 July 2002 (2002-07-04) claims 1,6; examples 1-8	1-13
A	WO 01/70675 A (METHYLGENE INC) 27 September 2001 (2001-09-27) claim 1; examples 52,64	1-13

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8 and 11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/JP2004/001438

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9414775	A1	07-07-1994	EP	0677043	A1	18-10-1995
			JP	8505846	T	25-06-1996
			US	5726192	A	10-03-1998
WO 0226696	A	04-04-2002	AU	9013401	A	08-04-2002
			CA	2423868	A1	04-04-2002
			EP	1335898	A1	20-08-2003
			WO	0226696	A1	04-04-2002
			JP	2004509941	T	02-04-2004
			US	2004092598	A1	13-05-2004
US 2003018062	A1	23-01-2003	US	2004024067	A1	05-02-2004
			AU	8212901	A	26-03-2002
			BR	0113669	A	03-06-2003
			CA	2420899	A1	21-03-2002
			CN	1450991	T	22-10-2003
			CZ	20030573	A3	18-06-2003
			WO	0222577	A2	21-03-2002
			EP	1318980	A2	18-06-2003
			HU	0300880	A2	28-08-2003
			JP	2004509105	T	25-03-2004
			NO	20030867	A	25-02-2003
			SK	2422003	A3	11-09-2003
WO 02051842	A	04-07-2002	BR	0116402	A	11-11-2003
			CA	2431471	A1	04-07-2002
			CN	1483033	T	17-03-2004
			CZ	20031940	A3	15-10-2003
			WO	02051842	A1	04-07-2002
			EP	1353921	A1	22-10-2003
			NO	20032830	A	04-08-2003
			SK	9122003	A3	03-02-2004
			US	2004053960	A1	18-03-2004
WO 0170675	A	27-09-2001	AU	4870101	A	03-10-2001
			CA	2404002	A1	27-09-2001
			EP	1280764	A2	05-02-2003
			WO	0170675	A2	27-09-2001
			JP	2003528074	T	24-09-2003
			US	2002115826	A1	22-08-2002